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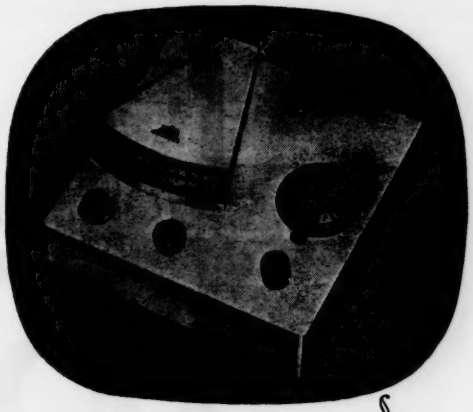

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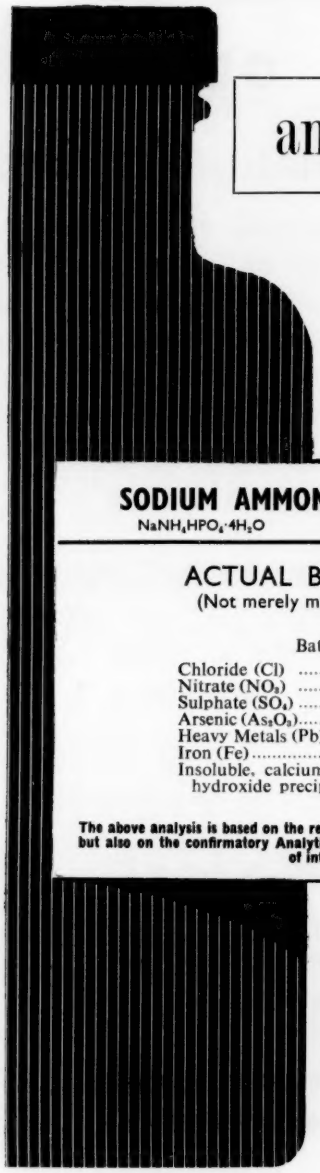

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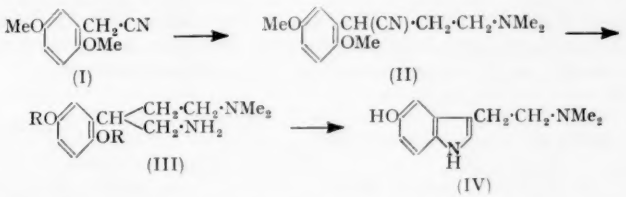
Hydroxytryptamines. Part I. Bufotenine, 6-Hydroxybufotenine, and Serotonin.

By JOHN HARLEY-MASON and A. H. JACKSON.

[Reprint Order No. 4804.]

Convenient syntheses of bufotenine and serotonin involving the ferricyanide oxidation of 2-(2 : 5-dihydroxyphenyl)-4-dimethylamino- and -4-amino-butylamine, respectively, are described. A similar synthesis gave 6-hydroxybufotenine, while attempts to isolate 6-hydroxyserotonin were unsuccessful.

IT has been shown (Cromartie and Harley-Mason, *J.*, 1952, 2525) that ferricyanide oxidation of 2-(2 : 5-dihydroxyphenyl)ethylamine gives 5-hydroxyindole in high yield. Application of this reaction to the synthesis of 5-hydroxytryptamine derivatives of physiological interest is now described. Wieland, Konz, and Mittasch (*Ann.*, 1934, **513**, 1) isolated bufotenine, 5-hydroxy-*NN*-dimethyltryptamine (IV), from the skin of the common toad and determined its structure; more recently it has also been obtained from the fungus *Amanita mappa* (Wieland and Motzel, *Ann.*, 1953, **581**, 10). It was first synthesised by Hoshino and Shimodaira (*Ann.*, 1935, **520**, 19). 2 : 5-Dimethoxybenzyl cyanide (I), required as starting product for a new synthesis (previously described in outline, *Chem. and Ind.*, 1952, 954), was obtained from 2 : 5-dimethoxybenzaldehyde (Gattermann, *Ann.*, 1907, **357**, 369) by catalytic hydrogenation to the alcohol, which was converted into the chloride by thionyl chloride; the chloride was then treated with potassium cyanide. Alkylation of (I) with 2-dimethylaminoethyl chloride (cf. Eisleb, *Ber.*, 1941, **74**, 1433) and sodamide gave 1-(2 : 5-dimethoxyphenyl)-3-dimethylaminopropyl cyanide (II) which was then hydrogenated to 2-(2 : 5-dimethoxyphenyl)-4-dimethylaminobutylamine (III ; R = Me) :



Boiling this with hydrobromic acid gave the hydroxy-diamine (III, R = H), which on oxidation with potassium ferricyanide gave bufotenine (IV) in good yield. The reactions involved in this oxidation have been discussed earlier (Harley-Mason, *Chem. and Ind.*, 1952, 173; Cromartie and Harley-Mason, *loc. cit.*). The ultra-violet absorption spectrum is recorded in the Figure.

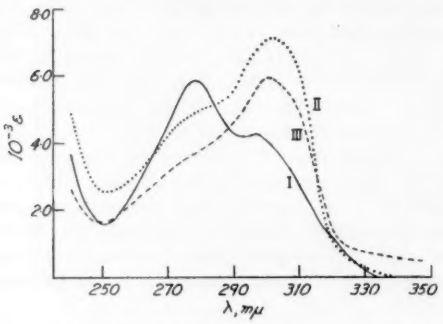
A similar reaction sequence was employed for 6-hydroxybufotenine [5 : 6-dihydroxy-*NN*-dimethyltryptamine (VI)]. In this case, the starting material, 2 : 4 : 5-trimethoxybenzyl cyanide, was obtained *via* the rhodanine condensation product of 2 : 4 : 5-trimethoxybenzaldehyde (cf. Julian and Sturgis, *J. Amer. Chem. Soc.*, 1935, **57**, 1126, 2739), since attempts to convert 2 : 4 : 5-trimethoxybenzyl alcohol into the corresponding chloride were unsuccessful. The trihydroxy-diamine (V) was obtained exactly as for (III), and a ferricyanide oxidation gave a rather low yield of (VI). The product was characterised as a picrate of rather unusual composition (2 mols. of base : 3 mols. of picric acid). Its identity was however confirmed by examination of its ultra-violet absorption spectrum (Figure), which was very similar to that of 5 : 6-dihydroxy-3-methylindole.

An alternative route to (VI), based on the observation (Harley-Mason, *J.*, 1953, 200) that 2-(2-amino-4 : 5-dihydroxyphenyl)ethylamine gives 5 : 6-dihydroxyindole on autoxidation, was explored. Alkylation of 3 : 4-dimethoxybenzyl cyanide (VII) with 2-dimethylaminoethyl chloride gave 3-dimethylamino-1-(3 : 4-dimethoxyphenyl)propyl cyanide

(VIII), which was readily nitrated to (IX). Catalytic hydrogenation followed by demethylation gave the dihydroxy-triamine (X). However, the yields of (VI) obtained on autoxidation or treatment with silver oxide of (X) were so low that this approach had to be abandoned.

(V) (VI)

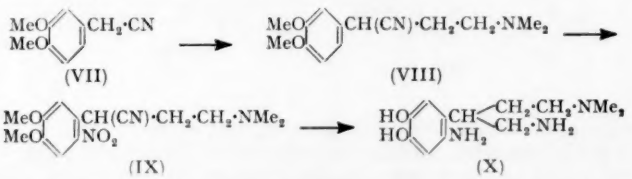
5-Hydroxytryptamine (XV) (serotonin, enteramine, thrombocytin) was isolated from ox serum by Rapport, Green, and Page (*J. Biol. Chem.*, 1948, **174**, 735; **176**, 1237), and from *Octopus vulgaris* and *Discoglossus pictus* by Erspamer and Ottolenghi (*Experientia*, 1952, **8**, 31, 152; *J. Biol. Chem.*, 1952, **200**, 311). Its distribution and pharmacological properties have been extensively studied in recent years. Four syntheses of serotonin have been reported (Hamlin and Fischer, *J. Amer. Chem. Soc.*, 1951, **73**, 5007; Speeter,



Ultra-violet absorption spectra.

I. ——— *Bufotenine (in 95% ethanol).*
II. ····· *6-Hydroxybufotenine (in 95% ethanol).*
III. — — — *5 : 6-Dihydroxy-3-methylindole (in buffer,* pH 6·7).

Heinzelmann, and Weisblatt, *ibid.*, p. 5514; *Chem. Eng. News*, 1953, **31**, 3861; Asero, Colo, Erspamer, and Vercellone, *Ann.*, 1952, **576**, 69) all of which involve addition of a two-carbon side-chain to a 5-alkoxy- or -benzyloxy-indole by well-known methods.

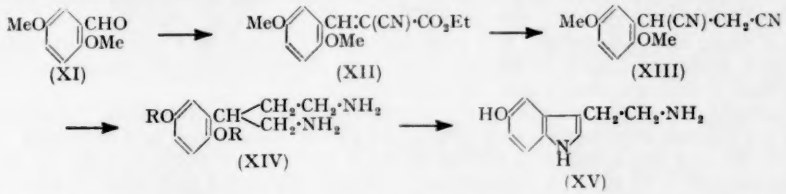


(VII) (VIII) (IX) (X)

Attempts to introduce a potential 2-aminoethyl side-chain into (I) by alkylation with *N*-2-bromoethylphthalimide or chloroacetonitrile were unsuccessful, so that an alternative route to the required diamine (XIV) was developed. 2 : 5-Dimethoxybenzaldehyde (XI) was condensed with ethyl cyanoacetate to give ethyl α-cyano-2 : 5-dimethoxycinnamate (XII) which when boiled with potassium cyanide gave 2 : 5-dimethoxyphenylsuccinonitrile (XIII) (cf. Mowry, *J. Amer. Chem. Soc.*, 1946, **68**, 2108). Catalytic hydrogenation of (XIII) in the presence of hydrochloric acid gave 1 : 4-diamino-2-(2 : 5-dimethoxyphenyl)butane (XIV; R = Me), from which (XIV; R = H) was obtained on treatment with hydrobromic acid. On ferricyanide oxidation the dihydroxy-amine gave serotonin (XV).

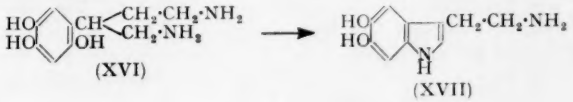
The overall yield of (XV) from (XI) was 25% and in view of its simplicity and of the few stages involved, this synthesis is recommended as the best available for serotonin. For pharmacological purposes serotonin has usually been isolated as the double salt with creatinine sulphate. We have found that the hydrogen oxalate is a more readily prepared crystalline salt and is stable and non-hygroscopic. It is noteworthy that oxidative ring-closure of (XIV; R = H) could theoretically lead either to an indole or a dihydroquinoline

derivative depending on which of the two amino-groups was involved; however, no indication of the formation of the latter was found.



(XI) (XII) (XIII) (XIV) (XV)

A similar reaction sequence from 2 : 4 : 5-trimethoxybenzaldehyde was used in an attempt to prepare 6-hydroxyserotonin (XVII). The trihydroxy-diamine (XVI) was obtained in exactly the same manner as (XIV), and the initial stage of oxidation with potassium ferricyanide appeared to proceed normally. However, attempts to isolate a pure product were unsuccessful, though the extracts gave a strongly positive Ehrlich reaction similar to that given by (VI).



(XVI) (XVII)

Experimental

2 : 5-Dimethoxybenzyl Cyanide.—2 : 5-Dimethoxybenzaldehyde (15 g.) was hydrogenated in ethanol (150 c.c.) over platinum oxide (0·15 g.) at 50° and 50 atm. After filtration and removal of the solvent, 2 : 5-dimethoxybenzyl alcohol (13·2 g.) was distilled at 110°/1 mm. Thionyl chloride (20 c.c.) in ether (80 c.c.) was added during 15 min. to a solution of the above alcohol (13 g.) and pyridine (1 c.c.) in ether (150 c.c.) with stirring. After a further 15 min. the solution was extracted with water (2 × 100 c.c.) and dried ($MgSO_4$). Removal of the solvent and recrystallisation from light petroleum (b. p. 80—100°) gave 2 : 5-dimethoxybenzyl chloride (crude yield 13·1 g., 92%) as needles, m. p. 70—72°. Baumann and Fraenkel (*Z. physiol. chem.*, 1895, **20**, 20) give m. p. 72—73°.

A solution of the above chloride (12·5 g.) and potassium cyanide (30 g.) in ethanol (240 c.c.) and water (60 c.c.) was refluxed for 3 hr. The dark red solution was cooled and poured on ice (300 g.), and the oil extracted with ether. The ethereal extract was dried ($MgSO_4$) and the solvent removed. Distillation of the residue at 115°/2 mm. gave 2 : 5-dimethoxybenzyl cyanide (9·8 g.), large prisms, m. p. 52—53°. Sugasawa and Shigehara (*Ber.*, 1941, **74**, 459) give m. p. 54—55°.

1-(2 : 5-Dimethoxyphenyl)-3-dimethylaminopropyl Cyanide.—A solution of 2-dimethylaminoethyl chloride hydrochloride (8·7 g.) in water (25 c.c.) was treated with 2N-sodium hydroxide (30 c.c.), then saturated with potassium carbonate and extracted with benzene (3 × 15 c.c.). The dried (K_2CO_3) extracts were added to a solution of 2 : 5-dimethoxybenzyl cyanide (10·6 g.) in benzene (25 c.c.). Finely powdered sodamide (2·4 g.) was slowly added with stirring, the temperature being kept below 40°. The mixture was then heated under reflux on the water-bath with vigorous stirring for 2 hr. After cooling, the mixture was extracted with water to remove the separated sodium chloride, the benzene layer dried (K_2CO_3), and the solvent removed. The residual oil was distilled at 150—155°/2·5 mm. giving the amino-cyanide (7·5 g., 51%) as a pale yellow oil. A portion was treated with hydrogen chloride giving *1-(2 : 5-dimethoxyphenyl)-3-dimethylaminopropyl cyanide hydrochloride*, which formed white prisms from ethanol–ether, m. p. 161—162° with softening at 150° (Found : C, 59·3; H, 7·7; N, 9·6. $C_{14}H_{20}O_2N_2$,HCl requires C, 59·0; H, 7·4; N, 9·6%).

2-(2 : 5-Dihydroxyphenyl)-4-dimethylaminobutylamine (III; R = H).—A solution of the amino-cyanide (7 g.) in ethanol (50 c.c.) saturated with ammonia was hydrogenated over Raney nickel at 100° and 100 atm. for 5 hr. The catalyst was filtered off, the solvent removed, and the residual oil distilled at 145—150°/2·5 mm., giving the diamine (III; R = Me) (5·8 g.) as a pale yellow oil. The *dipicrate* formed yellow prisms, m. p. 198—199° (decomp.), from methanol (Found : C, 43·9; H, 4·2; N, 16·0. $C_{14}H_{24}O_2N_2,2C_6H_3O_7N_3$ requires C, 43·9; H, 4·2; N, 15·8%).

The dimethoxy-diamine (1·3 g.) was refluxed with hydrobromic acid (*d* 1·49; 8 c.c.) for 45 min., and the resulting solution diluted with water and evaporated to dryness on the water-bath under reduced pressure of hydrogen. The residual dark brown solid was dissolved in water and boiled with charcoal, and the solution again evaporated under hydrogen. The last traces of water and hydrobromic acid were removed by storage in a vacuum desiccator over phosphoric oxide and sodium hydroxide, leaving the dihydroxy-diamine dihydrobromide as a light brown hygroscopic glass which did not crystallise.

Bufotenine (IV).—To a solution of the dihydroxy-diamine dihydrobromide (1·9 g.) in water (60 c.c.), a solution of potassium ferricyanide (3·2 g.) and sodium hydrogen carbonate (1·65 g.) in water (60 c.c.) was added with stirring during 5 min. The mixture darkened at first, but became paler after 20 min. A little sodium dithionite was added and, after filtration from a small amount of flocculent precipitate, the light yellowish-brown solution was extracted continuously with peroxide-free ether for 2 days. Removal of the ether and drying of the residue in a vacuum over phosphoric oxide gave bufotenine (0·45 g.; 45%) as a hard brown glass, purified by sublimation at 160°/10^{-4} mm. The picrate formed red needles, m. p. 177° (decomp.), from methanol (Found : C, 43·6; H, 3·6; N, 17·2. Calc. for $C_{12}H_{16}ON_2,2C_6H_3O_7N_3$: C, 43·5; H, 3·3; N, 16·8%). Hoshino and Shimodaira (*loc. cit.*) give m. p. 178°.

2 : 4 : 5-*Trimethoxybenzyl Alcohol.*—2 : 4 : 5-Trimethoxybenzaldehyde (5 g.), dissolved in ethanol (100 c.c.), was hydrogenated over platinum oxide (0·2 g.), the reaction being interrupted when one mol. of hydrogen had been absorbed. After filtration from the catalyst, evaporation of the solvent left an oil from which 2 : 4 : 5-*trimethoxylbenzyl alcohol* was obtained as small prisms, m. p. 70—71°, after recrystallisation from benzene–light petroleum (Found : C, 60·5; H, 7·4. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%).

Reaction with Thionyl Chloride.—The above alcohol (1·5 g.), dissolved in dry ether (25 c.c.) and pyridine (0·1 c.c.), was treated with thionyl chloride (2·25 g.) in ether (10 c.c.). After 20 min. at room temperature the mixture was extracted with water (2 × 10 c.c.), the ethereal solution was dried (Na_2SO_4), and the solvent was removed. From the residue a halogen-free substance (1·2 g.), m. p. 101°, was isolated as prisms by recrystallisation from light petroleum (b. p. 80—100°) [Found : C, 65·1; H, 6·4; OMe, 45·3%; *M* (Rast), 287].

2 : 4 : 5-*Trimethoxybenzylidenerhodanine.*—Rhodanine (15 g.) and 2 : 4 : 5-trimethoxybenzaldehyde (15 g.) were dissolved in acetic acid (100 c.c.), finely powdered anhydrous sodium acetate (20 g.) was added, and the mixture refluxed for 4 hr. The mixture, from which most of the product had crystallised during the reaction, was poured into water, and the product filtered off and washed with water, alcohol, and ether. 2 : 4 : 5-*Trimethoxybenzylidenerhodanine* (12 g.) formed red needles, very sparingly soluble in most organic solvents. A small quantity recrystallised from glycol monoethyl ether had m. p. 250—252° (decomp.) (Found : C, 50·1; H, 4·1. $C_{13}H_{13}O_4NS_2$ requires C, 50·2; H, 4·1%).

2 : 4 : 5-*Trimethoxybenzyl Cyanide.*—The foregoing rhodanine derivative (12 g.) was warmed at 100° with 15% sodium hydroxide (80 c.c.) for 20—30 min. until it had all dissolved, giving a deep yellowish-brown solution, and the solution was then cooled. 10% Hydrochloric acid (120 c.c.) was added and the voluminous precipitate of the thiopyruvic acid was collected and dried. Sodium (2·7 g.) was dissolved in dry ethanol (80 c.c.) and added to hydroxylamine hydrochloride (8 g.) dissolved in water (8 c.c.). The sodium chloride was filtered off and the filtrate poured on to the thiopyruvic acid. The mixture was heated on the water-bath for 20 min. with stirring; a homogeneous solution was obtained. The alcohol was removed under vacuum the residue taken up in 5% sodium hydroxide (40 c.c.), and the solution filtered and cooled in ice. Addition of 10% hydrochloric acid precipitated 2 : 4 : 5-trimethoxyphenylpyruvic acid oxime, which was collected, washed, and dried. The oxime was treated with acetic anhydride (50 c.c.), and the mixture warmed continuously on the water-bath until all had dissolved. The acetic anhydride was then removed under vacuum and the residue was shaken with ether and water. The ethereal layer was separated, washed with sodium carbonate solution, and dried ($MgSO_4$). The solvent was removed and the residue distilled at 80—90°/10^{-4} mm. giving 2 : 4 : 5-trimethoxybenzyl cyanide (2·8 g.) as blunt needles, m. p. 84° [after recrystallisation from light petroleum (b. p. 80—100°)] (Found : N, 6·75. Calc. for $C_{11}H_{13}O_3N$: N, 6·8%). Robertson and Rusby (*J.*, 1935, 1371) give m. p. 85°.

3-*Dimethylamino*-1-(2 : 4 : 5-*trimethoxyphenyl*)*propyl Cyanide.*—2-Dimethylaminoethyl chloride hydrochloride (2 g.) dissolved in water (5 c.c.) was treated with 2N-sodium hydroxide (6·6 c.c.), and extracted with xylene (3 × 10 c.c.) after saturation with potassium carbonate. 2 : 4 : 5-Trimethoxybenzyl cyanide (2·5 g.) was dissolved in the dried (K_2CO_3) xylene extracts, and the solution cooled to 0° before the addition of powdered sodamide (0·54 g.). The mixture

was heated slowly to 100°, kept at this temperature for 30 min., and then boiled under reflux for 5 hr. The cooled solution was shaken with dilute hydrochloric acid (40 c.c.), and the aqueous layer separated and basified with sodium hydroxide before it was extracted with ether (3 × 25 c.c.). The dried ($MgSO_4$) ethereal extract was evaporated and the residual oil distilled from a small retort (external temperature 140°) at 0·1 mm., yielding a viscous yellow oil (1·5 g.). Treatment of a portion with hydrogen chloride gave *3-dimethylamino-1-(2 : 4 : 5-trimethoxyphenyl)propyl cyanide hydrochloride* as small white prisms, m. p. 172—174°, from ethanol–ether (Found : C, 57·4; H, 7·6; N, 8·9. $C_{15}H_{22}O_3N_2$,HCl requires C, 57·2; H, 7·4; N, 8·9%).

4-Dimethylamino-2-(2 : 4 : 5-trimethoxyphenyl)butylamine.—The foregoing amino-cyanide (1·5 g.), dissolved in dry ether (200 c.c.), was added slowly during 1 hr. to a stirred solution of lithium aluminium hydride (1 g.) in dry ether (50 c.c.). The mixture was refluxed for 2½ hr., cooled, and then decomposed with a saturated solution of sodium potassium tartrate (25 c.c.). The dried ($MgSO_4$) ether layer was evaporated, leaving the diamine as a yellow oil. Treatment of a portion with picric acid gave *4-dimethylamino-2-(2 : 4 : 5-trimethoxyphenyl)butylamine dipicrate* which formed yellow prisms, m. p. 187—190°, from methanol (Found : C, 43·6; H, 4·1; N, 14·6. $C_{15}H_{26}O_3N_2,2C_6H_3O_7N_3$ requires C, 43·8; H, 4·3; N, 15·1%). The diamine was demethylated as described above for the dimethoxy-compound (III; R = Me), giving the trihydroxy-diamine (V) dihydrobromide as a hygroscopic light brown glass.

6-Hydroxybufotenine (VI).—The above dihydrobromide (0·89 g.), dissolved in water (40 c.c.), was treated with a solution of potassium ferricyanide (1·32 g.) and sodium hydrogen carbonate (0·84 g.) in water (40 c.c.). The deep red solution was kept for 1·5 hr. under hydrogen, the colour changing to dark grey. A little sodium dithionite was added to prevent further oxidation, and a small amount of dark precipitate was filtered off. The solution was then continuously extracted with peroxide-free ether for 2 days. The extract, which showed a marked bluish-violet fluorescence, was evaporated and the residue dried in a vacuum over phosphoric oxide. Sublimation at 135°/10^{-4} mm. gave an almost colourless waxy solid of indefinite m. p. Its ultra-violet spectrum is given in the Figure. With Ehrlich's reagent it gave a bluish-green colour which slowly changed to a very intense blue. Treatment with methanolic picric acid gave *6-hydroxybufotenine picrate*, red needles, m. p. 139—140° (decomp.) (Found : C, 44·6; H, 4·1; N, 15·7. $2C_{12}H_{16}O_2N_2,3C_6H_3O_7N_3$ requires C, 45·3; H, 3·9; N, 16·0%).

1-(4 : 5-Dimethoxy-2-nitrophenyl)-3-dimethylaminopropyl Cyanide (IX).—3 : 4-Dimethoxybenzyl cyanide was alkylated with 2-dimethylaminoethyl chloride as described for the 2 : 5-dimethoxy-compound, except that xylene was used as solvent. 1-(3 : 4-Dimethoxyphenyl)-3-dimethylaminopropyl cyanide distilled at 115—120°/0·1 mm. and was characterised as the *picrate* which formed yellow prisms, m. p. 156—158°, from aqueous ethanol (Found : N, 14·8. $C_{14}H_{20}O_2N_2,C_6H_3O_7N_3$ requires N, 14·7%). The amino-cyanide (7 g.) was dissolved in dilute nitric acid (15 c.c.), and the solution added slowly with stirring and cooling to concentrated nitric acid (30 c.c.). After storage overnight at 0° the mixture was poured into water and basified with sodium hydroxide. The nitro-compound was extracted with ether and the extract dried (Na_2SO_4). After removal of the solvent the residue was taken up in ethanol (30 c.c.), and hydrogen chloride passed in. The precipitated *1-(4 : 5-dimethoxy-2-nitrophenyl)-3-dimethylaminopropyl cyanide hydrochloride* was collected and recrystallised from ethanol giving very pale yellow needles, m. p. 189—190° (decomp. with softening at 183°) (Found : C, 51·1; H, 6·3; N, 12·5. $C_{14}H_{20}O_4N_3Cl$ requires C, 51·0; H, 6·1; N, 12·7%).

2-(4 : 5-Dihydroxy-2-aminophenyl)-4-dimethylaminobutylamine (X).—The above hydrochloride (2·5 g.) dissolved in ethanol (225 c.c.) and 2N-hydrochloric acid (25 c.c.) was hydrogenated over platinum oxide (0·5 g.) at 4—5 atm. Hydrogen uptake was complete after 2·5 hr.; the catalyst was then filtered off and the solvent removed under reduced pressure of hydrogen at 40°. The pale blue residue was dried in a vacuum desiccator and then triturated with a small quantity of propanol and ether, which removed most of the colour. Recrystallisation from propanol–ether yielded *2-(4 : 5-dimethoxy-2-aminophenyl)-4-dimethylaminobutylamine trihydrochloride* (1·9 g.) as tiny needles, m. p. 237—239° (decomp.) (Found : N, 11·6. $C_{14}H_{25}O_2N_3$,3HCl requires N, 11·2%). The trihydrochloride was demethylated with hydrobromic acid as for (III; R = Me) above. The dihydroxy-trihydrobromide formed a pale greenish solid. Autoxidation or oxidation of this compound with silver oxide yielded only traces of 6-hydroxybufotenine.

Ethyl α-Cyano-2 : 5-dimethoxycinnamate.—2 : 5-Dimethoxybenzaldehyde (5·6 g.) and ethyl cyanoacetate (3·7 g.) were dissolved in warm ethanol (10 c.c.), piperidine (0·1 c.c.) was added, and the solution was kept at 60° for an hour. On cooling of the solution to 0°, *ethyl α-cyano-2 : 5-dimethoxycinnamate* (7·9 g., 95%) crystallised as beautiful orange needles, which were

collected and washed with a little alcohol. The bulk of the product was used directly for the next stage; for analysis, a small portion was recrystallised from aqueous ethanol, and had m. p. 81° (Found: C, 64·4; H, 5·8; N, 5·7. $C_{14}H_{15}O_4N$ requires C, 64·4; H, 5·8; N, 5·4%).

2 : 5-*Dimethoxyphenylsuccinonitrile* (XIII).—The foregoing ester (7·9 g.) and A.R. potassium cyanide were dissolved in 90% ethanol (120 c.c.), and the mixture refluxed for 2 hr. The resulting solution was cooled and filtered, the solvent was removed under reduced pressure of nitrogen, and the residue was twice recrystallised from aqueous ethanol, giving 2 : 5-*dimethoxyphenylsuccinonitrile* (4·6 g., 70%) as short white needles, m. p. 85° (Found: C, 66·5; H, 5·4; N, 13·1. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·5; N, 12·9%).

1 : 4-*Diamino*-2-(2 : 5-*dimethoxyphenyl*)*butane Dihydrochloride*.—The succinonitrile (4 g.), dissolved in ethanol (195 c.c.) and concentrated hydrochloric acid (5 c.c.), was hydrogenated at 4—5 atm. over platinum oxide (0·5 g.) Hydrogen uptake ceased after about 5 hr., and the solution was then filtered and evaporated under vacuum. The residual solid was triturated with a little propanol and ether, and then recrystallised from ethanol–ether. 1 : 4-*Diamino*-2-(2 : 5-*dimethoxyphenyl*)*butane dihydrochloride* (XIV; R = Me) (4·6 g., 85%) formed small prisms, m. p. 219—220° (decomp.) (Found: C, 48·7; H, 7·4; N, 9·3. $C_{12}H_{20}O_2N_2$,2HCl requires C, 48·5; H, 7·4; N, 9·4%).

Similar reduction of phenylsuccinonitrile (Mowry, *loc. cit.*) gave 1 : 4-*diamino*-2-*phenylbutane dihydrochloride*, m. p. 295—297° (decomp.) (Found: C, 51·1; H, 7·7; N, 12·0. $C_{10}H_{16}N_2$,2HCl requires C, 50·6; H, 7·6; N, 11·8%).

Demethylation.—The dimethoxy-diamine dihydrochloride (4 g.) was demethylated as for (III, R = Me); after the evaporation the residue was triturated with warm propanol and ether, and the 1 : 4-*diamino*-2-(2 : 5-*dihydroxyphenyl*)*butane dihydrobromide* (4·3 g., 90%) then crystallised. (On the first occasion, crystallisation was extremely slow; subsequently when seed-crystals were available, no difficulty was encountered.) Recrystallised from ethanol–ether, it formed prisms, m. p. 254—257° (decomp.) (Found: C, 33·6; H, 5·1; N, 7·5. $C_{10}H_{16}O_2N_2$,2HBr requires C, 33·5; H, 5·0; N, 7·8%).

Serotonin (XV).—The foregoing dihydrobromide (1·78 g.), dissolved in water (80 c.c.), was treated with a solution of potassium ferricyanide (3·2 g.) and sodium hydrogen carbonate (1·69 g.) in water (80 c.c.). The resulting greenish-brown solution was extracted with peroxide-free ether (300 c.c.) in a continuous extractor for 2 days; the aqueous solution had then become yellow and a small amount of amorphous precipitate had settled out, while the ether was almost colourless and a small amount of yellowish-brown oily material (*A*) had separated from it. The ethereal solution was decanted and evaporated under hydrogen, leaving crude serotonin as a brown gum. Sublimation of a portion at 150°/10^{-4} mm. gave serotonin as a very pale brown glass, which could not be crystallised. The bulk of the material was dissolved in a little warm ethanol and treated with an ethanolic solution of oxalic acid. A small amount of brownish amorphous solid was filtered off, and to the warm filtrate dry ether was added until the product began to separate. After being kept at 0°, the *serotonin* [*5-hydroxytryptamine*] *hydrogen oxalate* (0·55 g.), which had separated as pale buff micro-crystals, was collected. More (0·08 g.) of less pure material was obtained by treating the oily material (*A*) with ethanolic oxalic acid, the total yield being 0·63 g. (48%). A further recrystallisation from ethanol–ether (charcoal) gave a colourless product, m. p. 195—197° (decomp.) (Found: C, 54·3; H, 5·3; N, 10·6. $C_{10}H_{12}ON_2$,$C_2H_2O_4$ requires C, 54·1; H, 5·3; N, 10·5%). By treatment of serotonin with the calculated amount of ethanolic oxalic acid, *serotonin oxalate*, large plates, m. p. 194—196° (decomp.) from ethanol, was obtained (Found: C, 59·7; H, 5·85; N, 12·75. $2C_{10}H_{12}ON_2$,$C_2H_2O_4$ requires C, 59·7; H, 5·9; N, 12·7%). With Ehrlich's reagent a pinkish-violet colour was given initially, slowly becoming an intense deep blue. The ultra-violet absorption spectrum of the free base was found to agree with that reported by Hamlin and Fischer (*loc. cit.*). The picrate formed orange-red needles, m. p. 196—197° (decomp., with sintering at 130°) from aqueous methanol; Asero *et al.* (*loc. cit.*) give m. p. 191—193° (Found: C, 45·7; H, 4·3; N, 16·7 Calc. for $C_{10}H_{12}ON_2$,$C_6H_3O_7N_3$,H_2O: C, 45·4; H, 4·0; N, 16·6%).

Ethyl α-Cyano-2 : 4 : 5-*trimethoxycinnamate*.—2 : 4 : 5-Trimethoxybenzaldehyde (6·6 g.) and ethyl cyanoacetate (3·8 g.) were dissolved in ethanol (40 c.c.), and the warm solution treated with two drops of piperidine. The solution became bright yellow, heat was evolved, and the product rapidly crystallised. *Ethyl α-cyano*-2 : 4 : 5-*trimethoxycinnamate* (9 g.) formed feathery, bright yellow needles, m. p. 161°, from ethanol (Found: C, 62·3; H, 6·1; N, 4·8. $C_{15}H_{17}O_5N$ requires C, 61·8; H, 5·8; N, 4·8%).

1 : 4-*Diamino*-2-(2 : 4 : 5-*trihydroxyphenyl*)*butane* (XVI).—The foregoing ester (9·0 g.) was treated with potassium cyanide (4·0 g.) in ethanol (400 c.c.; 90%) as in the case of the di-

methoxy-compound (XII). 2 : 4 : 5-*Trimethoxyphenylsuccinonitrile* formed needles, m. p. 107°, from aqueous ethanol (Found : N, 11·5. $C_{13}H_{14}O_3N_2$ requires N, 11·4%). The nitrile was reduced in the same manner as the corresponding dimethoxy-compound, yielding 1 : 4-*diamino*-2-(2 : 4 : 5-*trimethoxyphenyl*)*butane dihydrochloride*, prisms, m. p. 248—250° (decomp.) (Found : C, 45·2; H, 7·2. $C_{13}H_{22}O_3N_2,2HCl,H_2O$ requires C, 45·2; H, 7·1%).

Demethylation was carried out as in the previous examples, giving 1 : 4-*diamino*-2-(2 : 4 : 5-*trihydroxyphenyl*)*butane dihydrobromide*, prisms, m. p. 229—231° (decomp.) (Found : C, 31·4; H, 5·2; N, 7·6. $C_{10}H_{16}N_2O_3,2HBr$ requires C, 31·8; H, 4·8; N, 7·5%). Oxidation with potassium ferricyanide or silver oxide gave a deep red solution : however, on continuous extraction with ether, only traces of material were obtained, though a strongly positive Ehrlich reaction indicated that a small amount of the expected product, 6-hydroxyserotonin (XVII) was probably formed.

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A New Synthesis of Pantethine and Some Analogues thereof.

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A synthesis of pantethine (II) has been evolved by the condensation of D(−)-pantolactone with di-(2-*N*-β-alanylamidoethyl) disulphide. By this general method, various analogues of pantethine have also been prepared.

PANTETHEINE, a growth factor of *Lactobacillus bulgaricus*, was first synthesised by Snell, Brown, Peters, Craig, Wittle, Moore, McGlohon, and Bird (*J. Amer. Chem. Soc.*, 1950, **72**, 5349) and later by Baddiley and Thain (*J.*, 1952, 800). It possesses the structure (I), interconvertible with the disulphide, pantethine (II).

$$HO{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(OH){\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}SH \quad (I)$$

$$[HO{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(OH){\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}S]_2 \quad (II)$$

The earlier synthesis (Snell *et al.*, *loc. cit.*) involved reaction between methyl pantothenate and 2-mercaptoethylamine, to give poor yields of (I) which was isolated only with difficulty. The synthesis due to Baddiley and Thain (*loc. cit.*) required simple condensation of D(−)-pantolactone (αγ-dihydroxy-ββ-dimethylbutyric lactone) with *N*-β-alanyl-2-mercaptoethylamine at 100°, substantially pure (I) being obtained.

Since this work was completed various other syntheses of pantethine have appeared.* Thus, novel methods have been described by Wieland and Bokelmann (*Naturwiss.*, 1951, **38**, 384), Schwyzer (*Helv. Chim. Acta*, 1952, **35**, 1903), King, Stewart, and Cheldelin (*J. Amer. Chem. Soc.*, 1953, **75**, 1290); and, in a preliminary communication, Viscontini, Adank, Merckling, Ehrhardt, and Karrer (*Helv. Chim. Acta*, 1953, **36**, 835) have announced the development of a synthesis similar to that described in this work. At the outset, however, only the earlier American route was known and since this gave poor yields it was decided to evolve a synthesis which besides giving a pure product could, by modification, be used to prepare analogues which might have enhanced growth-promoting or, possibly, reversed (bacteriostatic) properties. This was achieved by the preparation in good yield of the dihydrochloride of di-(2-*N*-β-alanylamidoethyl) disulphide (III) by the Sheehan and Frank's modification (*J. Amer. Chem. Soc.*, 1949, **71**, 1856) of the Gabriel phthalimido-method. Cystamine, di-2-aminoethyl disulphide (Mills and Bogert, *J. Amer. Chem. Soc.*, 1940, **62**, 1173), was treated with β-phthalimidopropionyl chloride in the presence of

* Mention of the present work has been made in a footnote to the paper of Wittle, Moore, Stipek, Peterson, McGlohon, Bird, Brown, and Snell (*J. Amer. Chem. Soc.*, 1953, **75**, 1694).

magnesium oxide to give the derivative (IV), which on fission with hydrazine hydrate in the usual manner followed by treatment with dilute hydrochloric acid gave (III).

$$(HCl,NH_2\cdot CH_2\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot S)_2 \quad \text{(III)}$$

$$[o\text{-}C_6H_4(CO)_2N\cdot CH_2\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot S]_2 \quad \text{(IV)}$$

Condensation of the free base of (III) with D(−)-pantolactone in the absence of solvent gave good yields of pantethine. Paper chromatography of this crude condensation product and detection with a sodium cyanide–sodium nitroprusside spray showed three spots having R_F values, 0·18, 0·47, and 0·78 respectively. The first two of these were of relatively low intensity, yet detection with ninhydrin showed the first two spots clearly with only a very faint indication of the third visible after prolonged heating. The spot of R_F 0·18 was shown to be due to unchanged di-(2-*N*-β-alanylamidoethyl) disulphide and that of R_F 0·78 to pantetheine. The spot of R_F 0·47, mentioned but unidentified both by Baddiley and Thain (*loc. cit.*) and by Schwyzer (*loc. cit.*), is considered to be due to the monosubstituted disulphide (V) arising by incomplete reaction of the D(−)-pantolactone and the amide.

$$\begin{matrix} HO\cdot CH_2\cdot CMe_2\cdot CH(OH)\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot S \\ NH_2\cdot CH_2\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot S \end{matrix} \quad \text{(V)}$$

By this means pantethine, having an activity of 22,600 units/mg. when tested as a growth stimulant for *Lactobacillus helveticus* 80, was obtained. This value was lower than obtain by Baddiley and Thain (*loc. cit.*) but, as these authors state, the accuracy of the microbiological method of testing is somewhat limited.

Simple analogues were prepared by this method by variation of the lactone moiety. In this manner, the corresponding γ-butyrolactone (VI; R = H) and γ-valerolactone (VI; R = Me) derivatives were obtained as colourless solids.

$$[R\cdot CH(OH)\cdot CH_2\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot S]_2 \quad \text{(VI)}$$

Barnett and Robinson (*Biochem. J.*, 1942, **36**, 357) have reported the preparation of 5-hydroxy-4 : 4-dimethylpent-2-enolactone (VII; R = H) by the condensation of β-hydroxy-αα-dimethylpropaldehyde with malonic acid under acid conditions followed by decarboxylation and lactonisation. Difficulty was experienced in repeating this work and an alternative method was sought by condensing the aldehyde with ethyl cyanoacetate (Cope's method, *J. Amer. Chem. Soc.*, 1941, **63**, 3452), to obtain 2-cyano-5-hydroxy-4 : 4-dimethylpent-2-enolactone (VII; R = CN). This on acid hydrolysis and decarboxylation gave the unsaturated lactone (VII; R = H) as an oil, which could be catalytically hydrogenated to the corresponding saturated lactone.

Silberstein (*Monatsh.*, 1904, **25**, 13), condensing the hydroxyaldehyde with malonic acid under ammoniacal conditions, reported a lactone (VII; R = H) as a crystalline solid, m. p. 177°; Barnett and Robinson (*loc. cit.*) also obtained a crystalline solid, m. p. 115°. By analogy with similar homologues the likelihood that a simple pentenolactone of this type should be a high-melting solid appears remote, and in neither case was hydrogenation to the corresponding saturated lactone attempted, as is reported in this work.

$$\begin{matrix} CH_2\cdot CMe_2\cdot CH{:}CR \\ O\text{———}CO \end{matrix} \quad \text{(VII)}$$

$$(HO\cdot CH_2\cdot CMe_2\cdot CH{:}CH\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot S)_2 \quad \text{(VIII)}$$

Condensation of (VII; R = H) with di-(2-*N*-β-alanylamidoethyl) disulphide gave the required analogue (VIII) as a resin; with the saturated lactone the corresponding analogue was obtained as a crystalline solid.

The first analogue of pantothenic acid found to be a growth inhibitor was *N*-pantoyltaurine, which was shown by Snell (*J. Biol. Chem.*, 1941, **139**, 975; 1941, **141**, 121) and almost simultaneously by Kuhn, Wieland, and Möller (*Ber.*, 1941, **74**, 1705) to inhibit the growth of lactic acid bacteria. Barnett and Robinson (*Biochem. J.*, 1942, **36**, 364) confirmed these findings and showed that the compound was active in inhibiting the growth *in vitro* of micro-organisms for which pantothenic acid was essential. With this in

mind, di-(2-*N*-taurylamidoethyl) disulphide (IX) was prepared by condensing 2-phthalimidoethane-1-sulphonyl chloride with cystamine, to give the derivative (X). This resisted

$(NH_2 \cdot CH_2 \cdot CH_2 \cdot SO_2 \cdot NH \cdot CH_2 \cdot CH_2 \cdot S)_2$ (IX)

$[o\text{-}C_6H_4(CO)_2N \cdot CH_2 \cdot CH_2 \cdot SO_2 \cdot NH \cdot CH_2 \cdot CH_2 \cdot S]_2$ (X)

$[HO \cdot CH_2 \cdot CMe_2 \cdot CH(OH) \cdot CO \cdot NH \cdot CH_2 \cdot CH_2 \cdot SO_2 \cdot NH \cdot CH_2 \cdot CH_2 \cdot S]_2$ (XI)

the normal removal of the phthaloyl groups by hydrazine hydrate but with boiling concentrated hydrobromic acid gave (IX) as the dihydrobromide. Condensation with D(−)-pantolactone gave the required analogue (XI) as a gum, which was purified by partition between *n*-butanol and water as in the case of pantethine.

Finally, modifications were made in the termination of the pantethine molecule. By using the homologue of cystamine, di-(4-aminobutyl) disulphide (Dirscherl and Weingarten, *Annalen*, **1951**, **574**, 131), the homologue (XII) was obtained as an amber resin, after purification by partition between *n*-butanol and water.

$[HO \cdot CH_2 \cdot CMe_2 \cdot CH(OH) \cdot CO \cdot NH \cdot CH_2 \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot S]_2$ (XII)

The anilide and dimethylamide of β-alanine were prepared by hydrogenation of the corresponding cyanoacetic acid derivatives in the presence of Raney nickel, being isolated as the hydrochloride and hydrobromide respectively. β-Alanine anilide was also obtained by the phthalimido-route from β-phthalimidopropionyl chloride and aniline, the phthaloyl group being removed with hydrazine hydrate. The free bases were condensed with D(−)-pantolactone to give, after the usual purification, pantothenic acid anilide as a crystalline solid and the dimethylamide as a resin.

Apart from pantethine itself, none of the analogues described above was significantly active in the promotion or inhibition of the growth of *Lactobacillus helveticus* 80.

Experimental

Except where otherwise stated the purification of the uncrystallisable analogues of pantethine was effected by counter-current distribution (13 tap funnels). The moving phase was the lower layer of the partitioning mixture which passed through the system and was collected on issuing from the last funnel. The process was continued until 12 lower layers had been collected.

Di-(2-β-alanylamidoethyl) Disulphide Dihydrochloride (III).—To a solution of cystamine (Mills and Bogert, *loc. cit.*) (7·6 g., 0·05 mole) in water (100 ml.) was added magnesium oxide (6 g., 0·15 mole), and the stirred suspension treated at 0° dropwise during 90 min. with a solution of β-phthalimidopropionyl chloride (24 g., 0·1 mole) in dry dioxan (180 ml.). The mixture was stirred at this temperature for 30 min.; N-hydrochloric acid (80 ml.) was then added during 15 min. The precipitated solid was filtered off, washed with water, and dried (22 g., 80%); m. p. 193—200°. Four crystallisations from chloroform–ethanol (1 : 4) gave colourless needles of *di-(2-β-phthalimidopropionamidoethyl) disulphide* (IV), m. p. 211—213° (Found: C, 56·2; H, 5·1; N, 9·7; S, 11·4. $C_{26}H_{26}O_6N_4S_2$ requires C, 56·3; H, 4·7; N, 10·1; S, 11·6%). Crude (IV) (19 g.) was refluxed for 3 hr. with hydrazine hydrate (3·4 g.) in ethanol (540 ml.). The suspension was cooled in ice-water and filtered, to give a white solid, m. p. >360° (10 g.). The filtrate on concentration *in vacuo* gave a gummy solid to which the previous product was added, and the mixture was shaken with 2N-hydrochloric acid (50 ml.) at room temperature for 2 hr. The suspension was cooled and filtered from phthalhydrazide, m. p. >360° (9 g.; theor., 11·1 g.). The filtrate was concentrated *in vacuo* to a gummy solid, which was dissolved in water (50 ml.) and warmed therein to 50°. Ethanol was added to incipient crystallisation; needles (4 g.) separated, having m. p. 204—207°. Concentration of the mother-liquor gave a less pure product (5 g.), m. p. 202—206° (total yield 72%). Three crystallisations from aqueous ethanol gave short needles of *di-(2-β-alanylamidoethyl) disulphide dihydrochloride*, m. p. 221—222° (Found: C, 33·0; H, 6·7; N, 14·9; S, 16·8; Cl, 18·9. $C_{10}H_{24}O_2N_4S_2Cl_2$ requires C, 32·7; H, 6·6; N, 15·3; S, 17·4; Cl, 19·3%).

Pantethine (I).—Di-(2-β-alanylamidoethyl) disulphide dihydrochloride (0·46 g.), suspended in absolute methanol (15 ml.), was treated with a 1·37N-solution of sodium methoxide in absolute methanol (1·85 ml.). To the clear solution was added D(−)-pantolactone (0·325 g.);

the solvent was evaporated and the residue kept in anhydrous conditions at 100° for 2·5 hr. The resulting clear glass was substantially pantethine and sodium chloride. Paper chromatography of the material with *n*-butanol–acetic acid–water (4 : 1 : 5) gave spots having R_F 0·78, 0·47, and 0·18, only the first of which was strong when detected with sodium cyanide–sodium nitroprusside spray. The glass was dissolved in aqueous *n*-butanol (15 ml.) and partitioned between *n*-butanol and water, the method outlined above being used. Paper chromatography of the various eluants and funnel contents showed the pantethine to lie in funnels 4—9 with no detectable impurity. The contents of these funnels were concentrated *in vacuo* to give pure pantethine as a colourless glass, $[\alpha]_D$ +15° (*c*, 3·2 in H_2O) (Found: C, 46·8; H, 7·4; N, 9·8; S, 10·9. Calc. for $C_{22}H_{42}O_8N_4S_2$: C, 47·6; H, 7·6; N, 10·1; S, 11·6%).

Di-(2-N′-4′-*hydroxybutyryl*-β-*alanylamidoethyl*) *Disulphide* (VI; R = H).—A suspension of (III) (3·67 g.) in absolute methanol (25 ml.) was treated with a 1·37N-solution of sodium methoxide in absolute methanol (14·6 ml.); to the clear solution was added γ-butyrolactone (1·72 g.) in absolute methanol (25 ml.), and the mixture refluxed for 3 hr., then concentrated *in vacuo* to a white solid, which was leached from sodium chloride with boiling absolute ethanol. Concentration of the extracts and cooling gave a white powder, m. p. 152—162° (1·5 g.), which on threefold crystallisation from absolute ethanol furnished the colourless *disulphide*, m. p. 192—193° (Found: C, 46·0; H, 7·4; N, 11·6; S, 13·3. $C_{18}H_{34}O_6N_4S_2$ requires C, 46·3; H, 7·3; N, 12·0; S, 13·7%).

Di-(2-N′-4′-*hydroxyvaleryl*-β-*alanylamidoethyl*) *Disulphide* (VI; R = Me).—By the method described in the preceding paragraph γ-valerolactone (2·0 g.) and (III) (3·67 g.) gave the required *product*, m. p. 177—179° (from absolute ethanol) (Found: C, 48·6; H, 7·5; N, 11·1; S, 12·7. $C_{20}H_{38}O_6N_4S_2$ requires C, 48·6; H, 7·7; N, 11·3; S, 13·0%.

2-*Cyano*-5-*hydroxy*-4 : 4-*dimethylpent*-2-*enolactone* (VII; R = CN).—To a solution of β-hydroxy-αα-dimethylpropaldehyde (61·2 g., 0·6 mole) in benzene (75 ml.) was added ethyl cyanoacetate (56·5 g., 0·5 mole), ammonium acetate (3·85 g., 0·05 mole), and glacial acetic acid (6·0 g., 0·1 mole), and the whole refluxed in an oil-bath (135°) under a Dean and Stark apparatus. Water was evolved immediately on boiling and within 1 hr. 12 ml. were collected. Refluxing was continued for a further hour and the mixture cooled, whereupon beautiful long needles of a substance separated (10 g.), m. p. 185°, which will be described in another communication. This material was filtered off, and the filtrate diluted with benzene (150 ml.), successively extracted with dilute aqueous sodium carbonate (2 × 50 ml.) and water (3 × 100 ml.), and dried (Na_2SO_4); the solvent was removed and the residue distilled *in vacuo*. A small initial fraction of the compound, m. p. 185°, sublimed followed by the major fraction, b. p. 166°/2 mm., which set to a solid (55 g.). Crystallisation from ethanol gave glistening plates of the *cyano-lactone*, m. p. 92° (Found: C, 63·8; H, 6·1; N, 9·5. $C_8H_9O_2N$ requires C, 63·6; H, 6·0; N, 9·3%). Ultra-violet absorption: max. at 255 mμ (ε 7078 in EtOH).

2-*Cyano*-5-*hydroxy*-4 : 4-*dimethylpentanolactone*.—Reduction of (VII; R = CN) (2 g.) in alcohol (50 ml.) over 10% palladised charcoal (0·2 g.) occurred smoothly at atmospheric pressure. Removal of the catalyst and concentration of the solution gave the saturated *lactone* as cubes (1·2 g.), m. p. 77—78° (Found: C, 62·9; H, 7·1; N, 8·9. $C_8H_{11}O_2N$ requires C, 62·7; H, 7·2; N, 9·1%).

5-*Hydroxy*-4 : 4-*dimethylpent*-2-*enolactone* (VII; R = H).—2-Cyano-5-hydroxy-4 : 4-dimethylpent-2-enolactone (10 g.) was refluxed for 18 hr. with constant-boiling hydrochloric acid (100 ml.), the solution was cooled and extracted with ether (3 × 50 ml.), the ethereal extracts were washed with water (3 × 50 ml.) and dried (Na_2SO_4), the ether was removed, and the residual oil was distilled *in vacuo*, to give the required *lactone* (4 g.), b. p. 52°/0·4 mm., n^{20} 1·4662 (Found: C, 66·8; H, 8·0. $C_7H_{10}O_2$ requires C, 66·6; H, 8·0%). Ultra-violet absorption: max. at 216 mμ (ε 7032 in H_2O containing 1% of EtOH).

5-*Hydroxy*-4 : 4-*dimethylpentanolactone*.—Hydrogenation of 5-hydroxy-4 : 4-dimethylpent-2-enolactone (5 g.), as in the previous example, gave the saturated *lactone* as an oil, b. p. 64°/0·7 mm., n^{20} 1·4520 (Found: C, 65·9; H, 9·8. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%), having no absorption in the range 215—300 mμ.

Di-[2-N′-(5′-*hydroxy*-4′ : 4′-*dimethylpent*-2′-*enoyl*)-β-*alanylamidoethyl*] *Disulphide* (VIII).—A suspension of (III) (0·736 g.) in methanol (20 ml.) was treated with a 1·37N-solution of sodium methoxide in methanol (2·92 ml.), followed by 5-hydroxy-4 : 4-dimethylpent-2-enolactone (0·504 g.) in methanol (20 ml.) under the conditions used in the preparation of pantethine. The resulting gum was dissolved in *n*-butanol (50 ml.) and washed with water saturated with *n*-butanol (15 × 20 ml.). Concentration of the organic layer gave a pale yellow glass which was substantially the required *analogue* (Found: C, 53·3; H, 8·4; N, 10·8; S, 12·8.

$C_{24}H_{42}O_6N_4S_2$ requires C, 52·7; H, 7·8; N, 10·2; S, 11·7%). Attempts to obtain a crystalline specimen by chromatographic or other means were unsuccessful.

Di-[2-N′-(5′-*hydroxy*-4′ : 4′-*dimethylpentanoyl*)-β-*alanylamidoethyl*] *Disulphide*.—A suspension of (III) (0·736 g.) in methanol was treated with sodium methoxide and 5-hydroxy-4 : 4-dimethylpentanolactone (0·512 g.) as for (VIII) above. The resulting resin was dissolved in *n*-butanol (50 ml.) and washed with water saturated with *n*-butanol (10 × 25 ml.). A further 50 ml. of *n*-butanol were then shaken with each aqueous washing, the resin thus being obtained in *n*-butanol solution, concentration of which gave the colourless *analogue*, crystallising from ether–ethanol as needles, m. p. 134—138° (Found: C, 52·8; H, 8·5; N, 9·9; S, 11·5. $C_{24}H_{46}O_6N_4S_2$ requires C, 52·3; H, 8·4; N, 10·2; S, 11·6%).

Di-(2-*taurylamidoethyl*) *Disulphide Dihydrobromide*.—To a solution of cystamine (0·76 g.) in dry dioxan (50 ml.) was added triethylamine (2·02 g.), followed at −5° by a solution of 2-phthalimidoethanesulphonyl chloride (2·73 g.) in dry dioxan (50 ml.) added dropwise during 1 hr. with stirring. The mixture was stirred at this temperature for a further hour, filtered from some amorphous material, and concentrated *in vacuo* to a gummy solid. Trituration under water gave a colourless solid (2·0 g.), m. p. 140—147°, which on two crystallisations from aqueous acetone gave feathery needles of *di*-(2-2′-*phthalimidoethylsulphonamidoethyl*) *disulphide*, m. p. 163—164° (Found: C, 46·0; H, 4·5; N, 9·1; S, 20·8. $C_{24}H_{26}O_6N_4S_4$ requires C, 46·0; H, 4·2; N, 8·9; S, 20·4%). For further synthetical work this was not purified but hydrolysed in the crude state with concentrated hydrobromic acid. It (2 g.) was refluxed for 90 min. with concentrated hydrobromic acid (25 ml.), cooled, diluted with water (15 ml.), cooled in ice-water, and filtered from phthalic acid. The filtrate was concentrated *in vacuo* to a brown oil, which on repeated crystallisation from aqueous ethanol gave light brown plates of the *disulphide dihydrobromide*, m. p. 170—173° (0·9 g.) (Found: C, 18·5; H, 4·7; N, 10·8; S, 24·2; Br, 30·0. $C_8H_{24}O_4N_4S_4Br_2$ requires C, 18·2; H, 4·6; N, 10·6; S, 24·3; Br, 30·3%).

Di-[2-N′-(D-2′ : 4′-*dihydroxy*-3′ : 3′-*dimethylbutyryltaurylamidoethyl*] *Disulphide* (XI).—A suspension of the foregoing dihydrobromide (1·06 g.) in absolute methanol (20 ml.) was treated with a 1·37N-solution of sodium methoxide in absolute methanol (2·96 ml.) and to the resulting clear solution was added D(−)-pantolactone (0·52 g.). The solvent was evaporated and the residual gum held at 100° for 3 hr. Examination of this material by paper chromatography with *n*-butanol–acetic acid–water (4 : 1 : 5) and detection with sodium cyanide–sodium nitroprusside revealed a major component having R_F 0·75 and two minor ones having R_F 0·46 and 0·23 respectively. By comparison with the pure substance, the last of these was shown to be due to di-(2-taurylamidoethyl) disulphide. When the spots on a duplicate paper were detected with ninhydrin only the two minor components were visible. Partition of the gum between *n*-butanol and water by the general method resulted in the analogue collecting in funnels 3—7. Concentration of these solutions gave the required *disulphide* as an uncrystallisable pale yellow glass, $[\alpha]_D$ +18° (*c*, 2·7 in H_2O) (Found: C, 39·0; H, 6·9; N, 8·7; S, 19·8. $C_{20}H_{42}O_{10}N_4S_4$ requires C, 38·3; H, 6·7; N, 8·9; S, 20·5%).

Di-(4-β-*alanylamidobutyl*) *Disulphide Dihydrochloride*.—Di-(4-aminobutyl) disulphide dihydrobromide (7·3 g.) (Dirscherl and Weingarten, *loc. cit.*), dissolved in water (100 ml.), was treated with magnesium oxide (2·4 g.) and, dropwise during 1 hr. at 0—5°, with β-phthalimidopropionyl chloride (9·6 g.) in dry dioxan (80 ml.). The mixture was stirred at this temperature for 30 min., then N-hydrochloric acid (100 ml.) was added, and the whole was stirred for 15 min., diluted with water (100 ml.), and filtered. The colourless solid crystallised from ethanol to give small needles of *di*-(4-*phthalimidopropionamidobutyl*) *disulphide*, m. p. 175° (Found: C, 59·1; H, 5·6; N, 9·4; S, 10·4. $C_{30}H_{34}O_6N_4S_2$ requires C, 59·0; H, 5·6; N, 9·2; S, 10·5%).

The phthaloyl groups were removed from this compound as for (III), and the resulting *di*-(4-β-*alanylamidobutyl*) *disulphide dihydrochloride* crystallised from ethanol–ether as needles, m. p. 159—160° (Found: C, 39·7; H, 7·6; N, 13·2; S, 15·1; Cl, 17·0. $C_{14}H_{32}O_2N_4S_2Cl_2$ requires C, 39·7; H, 7·5; N, 13·2; S, 15·1; Cl, 16·8%).

Di-[4-N′-(D-2′ : 4′-*dihydroxy*-3′ : 3′-*dimethylbutyryl*)-β-*alanylamidobutyl*] *Disulphide* (XII).—By the method given above for pantethine (II), the foregoing dihydrochloride (0·53 g.) was treated with sodium ethoxide and then coupled with D(−)-pantolactone (0·325 g.). The resultant gum on paper chromatography [pentan-1-ol–acetic acid–water (4 : 1 : 5)] showed spots having R_F 0·82, 0·40, and 0·09 respectively, detected with sodium cyanide–sodium nitroprusside; with ninhydrin only the last two spots were apparent. Partitioning as above between *n*-butanol and water gave the required *analogue* which was found chromatographically pure in the first three funnels and recovered as a pale yellow resin, $[\alpha]_D$ +12° (*c*, 1·3 in H_2O) (Found: C, 51·7; H, 8·4; N, 8·9; S, 10·3. $C_{26}H_{50}O_8N_4S_2$ requires C, 51·1; H, 8·3; N, 9·2; S, 10·5%).

β-*Alanine Anilide Hydrochloride.*—(*a*) A solution of cyanoacetanilide (5 g.) in alcohol (200 ml.) was shaken at 40° with Raney nickel (W7) in the presence of hydrogen at atmospheric pressure, the theoretical volume of hydrogen being rapidly absorbed. The filtered solution was concentrated *in vacuo* to an oil, which was dissolved in a ethanolic N-hydrochloric acid (30 ml.). On addition of ether to turbidity, β-*alanine anilide hydrochloride* crystallised as plates (4 g.), m. p. 201—202° (Found: C, 53·9; H, 6·8; N, 13·8; Cl, 17·8. $C_9H_{13}ON_2Cl$ requires C, 53·9; H, 6·5; N, 14·0; Cl, 17·7%).

(*b*) To a stirred suspension of aniline (1·86 g.) in water (25 ml.) at 10° was added a solution of β-phthalimidopropionyl chloride (4·75 g.) in dry dioxan (30 ml.) dropwise during 30 min., simultaneously with N-sodium hydroxide (20 ml.). The mixture was stirred for 15 min., poured into water (250 ml.), and filtered and the resulting solid crystallised from chloroform–ethanol (1 : 4), to give glistening needles (3·6 g.) of β-*phthalimidopropionanilide*, m. p. 191—192° (Found: C, 69·5; H, 4·7; N, 9·7. $C_{17}H_{14}O_3N_2$ requires C, 69·4; H, 4·8; N, 9·5%). Reaction of this compound in the usual manner with hydrazine hydrate followed by treatment with hydrochloric acid gave β-alanine anilide hydrochloride, m. p. 201—202°, identical with that prepared as above.

N-D-2 : 4-*Dihydroxy*-3 : 3-*dimethylbutyryl*-β-*alanine Anilide.*—β-Alanine anilide hydrochloride (0·8 g.) in absolute methanol (20 ml.) was treated with methanolic 1·37N-sodium methoxide (2·96 ml.) and then with D(−)-pantolactone (0·52 g.); the solvent was evaporated and the residual gum held at 100° for 3 hr. The gum was cooled, dissolved in the upper layer from *n*-butanol–acetic acid–water (4 : 1 : 5) (30 ml.), and washed successively with small quantities (12 × 20 ml.) of the lower layer of this mixture; these washings were washed twice with more of the upper layer (30 ml.). Evaporation then gave a resin which on trituration under ether gave a colourless solid, m. p. 101—104° (0·35 g.). This on crystallisation from ethyl acetate gave D-*pantothenanilide* as thick needles, m. p. 106—108°, $[\alpha]_D$ +7° (*c*, 6·5 in H_2O) (Found: C, 60·9; H, 7·6; N, 9·5. $C_{15}H_{22}O_4N_2$ requires C, 61·2; H, 7·5; N, 9·5%).

NN-*Dimethylcyanoacetamide.*—Ethyl cyanoacetate (56·5 g.) was treated with a solution of dimethylamine (45 g.) in ethanol (100 ml.) containing sodium ethoxide (0·5 g.) at room temperature for 3 days. The solution was concentrated *in vacuo* to a brown oil which crystallised from ethanol (50 ml.) at −30°. Recrystallisation from benzene–light petroleum (b. p. 40—60°) gave glistening plates of the *dimethylamide*, m. p. 65—66° (Found: C, 54·0; H, 7·1; N, 25·0. $C_5H_8ON_2$ requires C, 53·6; H, 7·2; N, 25·0%).

β-*Alanine Dimethylamide Hydrobromide.*—Reduction of the foregoing amide (2·7 g.) in ethanol with Raney nickel (W7) as described above for β-alanine anilide gave an oil. This was treated with a dilute solution of hydrobromic acid in ethanol, and ether was added to turbidity. Needles (2 g.) of the *hydrobromide*, m. p. 169—170°, were obtained (Found: C, 30·5; H, 6·6; N, 14·3; Br, 40·4. $C_5H_{13}ON_2Br$ requires C, 30·5; H, 6·7; N, 14·2; Br, 40·6%).

N-(D-2 : 4-*Dihydroxy*-3 : 3-*dimethylbutyryl*)-β-*alanine Dimethylamide.*—β-Alanine dimethylamide hydrobromide (0·79 g.) was treated with 1·37N-sodium methoxide (2·96 ml.) and kept at 100° with D(−)-pantolactone (0·52 g.) for 3 hr. The resulting gum when subjected to paper chromatography (*n*-butanol–acetic acid; ninhydrin) gave only one spot, due to β-alanine dimethylamide, having R_F 0·40. When the paper was kept in the dark for some weeks or heated to 130° for 20 min. a second spot, due to the analogue, appeared having R_F 0·75. The gum was partitioned between *n*-butanol and water as described above, NN-*dimethyl*-D-*pantothenamide*, $[\alpha]_D$ +22° (*c*, 2 in H_2O), being obtained as an almost colourless resin on concentration of the contents of funnels 10—12 (Found: C, 52·9; H, 8·9; N, 10·8. $C_{11}H_{22}O_4N_2$ requires C, 53·6; H, 9·0; N, 11·4%).

The authors thank Mr. G. I. Smailes for ultra-violet spectra determinations, Dr. O. D. Bird for microbiological examination of the analogues, and Mr. C. S. Franklin for valuable technical assistance.

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*The Reactions of Highly Fluorinated Organic Compounds. Part V.** 1H : 2H-*Hexafluoro*cyclo*butane and* 1H-*Pentafluoro*cyclo*but*-1-*ene.†

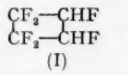
By M. W. Buxton and J. C. Tatlow.

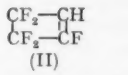
[Reprint Order No. 4855.]

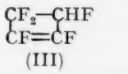
1 : 2-Dichlorohexafluoro*cyclo*butane gives, with lithium aluminium hydride, 1*H* : 2*H*-hexafluoro*cyclo*butane. Dehydrofluorination of this affords 1*H*-pentafluoro*cyclo*but-1-ene, as is shown by the formation of tetrafluorosuccinic acid upon oxidation.

This paper describes the treatment of 1 : 2-dichlorohexafluoro*cyclo*butane with lithium aluminium hydride, which was found to replace the chlorine of chloroperfluoro*cyclo*hexanes by hydrogen (Tatlow and Worthington, *J.*, 1952, 1251, and unpublished work). 1 : 2-Dichlorohexafluoro*cyclo*butane is readily made by heat-catalysed dimerisation of chlorotrifluoroethylene (Henne and Ruh, *J. Amer. Chem. Soc.*, 1947, **69**, 279; Harmon, U.S.P. 2,404,374; Buxton, Ingram, Smith, Stacey, and Tatlow, *J.*, 1952, 3830; Lacher, Tompkin, and Park, *J. Amer. Chem. Soc.*, 1952, **74**, 1693). Material made in this way has been shown to be mainly the *cis*-1 : 2-dichloride, and that from addition of chlorine to hexafluoro*cyclo*butene to be mainly the *trans*-isomer (Lacher, Büchler, and Park, *J. Chem. Phys.*, 1952, **20**, 1014).

Because it was thought that the boiling point of the corresponding dihydro-compound would be close to that of diethyl ether, the reaction of the dichloride with lithium aluminium hydride was first studied in di-*n*-butyl ether and in tetrahydrofuran. Though most of the chlorine was replaced, it was difficult to obtain a pure product if these ethers were used as solvents. In diethyl ether, however, a smooth reaction occurred, virtually all of the chlorine was eliminated, and the product, 1*H* : 2*H*-hexafluoro*cyclo*butane † (I) (b. p. 27°), could be separated from the solvent by fractional distillation. The reaction may proceed more readily in diethyl ether because of the greater solubility of lithium aluminium hydride in this solvent.


(I)


(II)


(III)

As with polyfluoro*cyclo*hexanes (Tatlow and Worthington, *loc. cit.*), the hexafluoro*cyclo*butane (I) was found to be susceptible to attack by concentrated aqueous potassium hydroxide. The product was a pentafluoro*cyclo*butene, as was confirmed by the amount of fluoride ion that appeared in the aqueous phase, corresponding to the elimination of one molecule of hydrogen fluoride. Addition of bromine across the double bond gave the corresponding dibromopentafluoro*cyclo*butane.

The olefin, of which a likely method of formation is the loss of fluoride ion from an intermediate carbonium anion resulting from separation of hydrogen under the influence of alkali, could have been either (II) or (III), depending upon whether, in the dehydrofluorination reaction, fluorine was eliminated from the $\cdot CF_2\cdot$ or the $\cdot CHF\cdot$ group flanking the $\cdot CHF\cdot$ function which provided the hydrogen. It is quite likely that such isomers would have very similar boiling points.

Oxidation of the olefin with aqueous potassium permanganate afforded only tetrafluorosuccinic acid, identified as the dianilinium salt (yield *ca.* 80%) and as the diamide. This strongly indicates that the olefin had the 1*H*-pentafluoro*cyclo*butene structure (II) and not the 3*H*-structure (III). It is possible that it contained a small proportion of (III) since the product (the unknown trifluorosuccinic acid) of the oxidation of this might be unstable, by analogy with other acids having fluorine atoms in the β-position and a hydrogen atom in the α-position relative to a carboxyl group (Henne and Zimmerschied, *J. Amer. Chem. Soc.*, 1947, **69**, 281; Buxton, Stacey, and Tatlow, *J.*, 1954, 366). However, in view of the

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† For this use of *H* to denote residual hydrogen atoms see *J.*, 1953, 5059.

volatility of the olefin, and of the fact that the optimum yield in the oxidation process may fall short of the theoretical, the identity of the olefin seems reasonably established.

Hence, in this particular dehydrofluorination reaction, hydrogen fluoride is eliminated preferentially from two adjacent ·CHF· groups, the flanking ·CF_2· groups being more resistant to the removal of fluorine. It is hoped that studies upon other types of fluorohydrocarbons will reveal more about the general characteristics of this type of process.

Experimental

1H : 2H-*Hexafluoro*cyclo*butane*.—1 : 2-Dichlorohexafluoro*cyclo*butane [140 g.; b. p. 59° (made by dimerisation of chlorotrifluoroethylene)] was added continuously during 4 hr. to a mechanically stirred suspension of lithium aluminium hydride (30 g.) in diethyl ether (1000 c.c.), at *ca.* 10°, in an apparatus having a trap cooled by solid carbon dioxide–alcohol on the exit line, moisture being excluded throughout. After the addition, the mixture was refluxed for 3 hr. and was left at 10—15° for 16 hr. It was cooled in ice, and water was added very cautiously and then sulphuric acid, until the metallic hydroxides had dissolved. The ethereal layer, an ethereal extract of the aqueous phase, and the contents of the cold trap were combined and dried ($MgSO_4$ followed by P_2O_5). Care was taken during the whole operation to avoid, as far as possible, losses of volatile material. Analysis of the aqueous layer showed that 96% of the chlorine contained in the starting material was present in the ionic form. Distillation of the ethereal layer gave 1H : 2H-*hexafluoro*cyclo*butane* (36·7 g.), b. p. 26·6—27·0° (Found : F, 68·8%; *M*, 162. $C_4H_2F_6$ requires F, 69·5%; *M*, 164), and a fraction (34·5 g.), b. p. 27·0—33·5°, consisting of a mixture of this compound and ether, which was combined with similar material and re-fractionated to give more product.

Dehydrofluorination of the Dihydro-compound.—The above hexafluoro*cyclo*butane (20·0 g.) and a solution of potassium hydroxide (45 g.) in water (30 c.c.) were stirred together mechanically at 15° for 5½ hr. in an apparatus which included a trap cooled by solid carbon dioxide–alcohol. The mixture was cooled in ice-water, and water (20·0 c.c.) was added. Whilst still cold, the organic phase was separated, combined with the contents (*ca.* 1 c.c.) of the cold trap, and washed quickly with ice-cold water. Analysis of the aqueous phase for fluoride ion by the method of Belcher, Caldas, Clark, and Macdonald (*Mikrochim. Acta*, 1953, 283) showed that 17·6% of the fluorine present in the parent compound had been removed (required for elimination of one fluorine from $C_4H_2F_6$, 16·7%). The organic phase was distilled from phosphoric oxide to give 1H-*pentafluoro*cyclo*but*-1-*ene* (11·2 g.), b. p. 25—26° (Found : F, 66·5. C_4HF_5 requires F, 65·95%).

Addition of Bromine to the Cyclic Olefin.—The 1*H*-olefin (2·99 g.) and bromine (1·2 c.c.), in a quartz vessel carrying a reflux condenser cooled by solid carbon dioxide, were irradiated with ultra-violet light for 6½ hr. The mixture was washed with aqueous sodium thiosulphate, then with water, and was distilled from phosphoric oxide to give 1H-1 : 2-*dibromopentafluoro*cyclo*butane* (2·45 g.), b. p. 107—109° (Found : C, 16·1; H, 0·5; Br, 52·6; F, 31·1. $C_4HBr_2F_5$ requires C, 15·8; H, 0·3; Br, 52·6; F, 31·3%). When this product was warmed with aqueous alkali, both bromide and fluoride ions appeared in the aqueous phase.

Oxidation of the Cyclic Olefin.—The olefin (2·35 g.), potassium permanganate (15·0 g.), and water (50 c.c.) were sealed into a cooled autoclave which was then shaken at 75—80° for 12 hr. The solution was filtered, and the filtrate and washings were treated with sulphur dioxide, filtered again, acidified (H_2SO_4), and extracted exhaustively with ether. The extract was dried ($MgSO_4$), filtered, and evaporated, and the residue was dried at 80°/30 mm. The crude acidic product was dissolved in dry ether (30 c.c.), aniline (4·0 g.) in ether (30 c.c.) was added, and when precipitation was complete, the dianilinium tetrafluorosuccinate (4·84 g.), m. p. 223—224° (Found : equiv., 190), was filtered off. After two recrystallisations from ethyl alcohol–chloroform, the salt (recovery 64%) had m. p. 224—225° (Found : C, 50·8; H, 4·4; F, 20·3%; equiv., 190. Calc. for $C_{16}H_{16}O_4N_2F_4$: C, 51·1; H, 4·3; F, 20·2%; equiv., 188).

This salt (1·04 g.) and ethyl alcohol (4·0 c.c.), containing fluorosulphonic acid (0·5 c.c.), were refluxed together for 30 min. The solution was poured into ice-water, the lower layer was extracted with ether, the extracts were dried ($MgSO_4$) and filtered, and the volume was reduced to 25 c.c. Ammonia was passed through, and after 16 hr. at 10—15° the precipitate (0·44 g.) was filtered off and recrystallised from water to give tetrafluorosuccinamide (0·19 g.), m. p. 259° (Found : C, 25·3; H, 2·2; F, 40·5. Calc. for $C_4H_4O_2N_2F_4$: C, 25·5; H, 2·1; F, 40·4%). Buxton, Ingram, Smith, Stacey, and Tatlow (*loc. cit.*) report m. p. 224° for the aniline salt, and

Henne and Zimmer (*J. Amer. Chem. Soc.*, 1951, **73**, 1103) give m. p. 259·8—260·3° for the amide. An oxidation of the olefin in a sealed tube gave a similar result.

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The Structure of Metrosiderene.

By R. E. CORBETT and W. G. HANGER.

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(−)-Metrosiderene, one of the sesquiterpenes present in the essential oils of *Metrosideros umbellata* and *Dacrydium biforme*, is shown to be a mixture of the isomers (I) and (II).

THE essential oil of *Metrosideros umbellata*, a tree endemic to New Zealand, was examined by Gardner (*J. Soc. Chem. Ind.*, 1931, **50**, 142T), who made a preliminary study of the dextrorotatory sesquiterpene fraction. By a precise fractionation Corbett and Hanger (*J. Sci. Food Agric.*, 1953, **4**, 508) isolated (+)-aromadendrene, (+)-cadinene, and a third sesquiterpene, to which the name (−)-metrosiderene is assigned.

This communication deals with metrosiderene. This has also been isolated from the essential oil of *Dacrydium biforme* (Corbett and Wong, unpublished work), the identity being established by comparison of their physical constants (see Table) and by the identity of their infra-red spectra.

B. p.	n_D^{20}	d_4^{20}	$[\alpha]_D^{20}$	$[R_L]_D$	Source
98°/3 mm.	1·5041	0·9155	−8·05°	66·1	*M. umbellata*
100°/4 mm.	1·5050	0·9148	−2·00	66·13	*D. biforme*

Analysis confirms the molecular formula $C_{15}H_{24}$. The sesquiterpene yields a dimeric crystalline nitrosate, by which it may be identified, and which is of unusual structure as it has the formula $C_{30}H_{48}O_{12}N_6$.

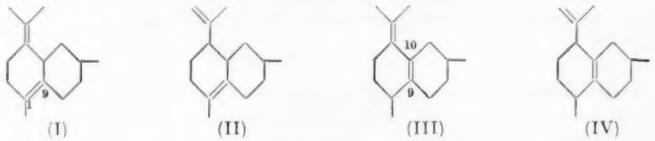
The molecular refraction is in agreement with that for a dicyclic sesquiterpene; this was confirmed by the preparation of an oily monohydrochloride which is unsaturated (nitromethane), and by consumption of 1·85 mols. of hydrogen in presence of Adams's platinum oxide. Further the sesquiterpene absorbed *ca.* 2 atoms of oxygen from perbenzoic acid. On dehydrogenation with selenium it yielded cadalene, and the infra-red spectrum of tetrahydrometrosiderene is identical with that of tetrahydro*iso*zingiberene, which Sorm *et al.* (*Chem. Listy*, 1952, **46**, 410) have shown to be a stereoisomer of cadinane. Stereochemically metrosiderene must be related to calacorene and *iso*zingiberene rather than to the various isomers of cadinene (Sorm *et al.*, *loc. cit.*).

Quantitative ozonolysis of the sesquiterpene of $[\alpha]_D^{20}$ −2·0° gave acetone (0·30 mol.), formaldehyde (0·30 mol.) and formic acid (0·28 mol.), indicating the presence of 30% of a hydrocarbon containing an *iso*propylidene group and 58% of one with an *iso*propenyl group. Sorm *et al.* (*Coll. Czech. Chem. Comm.*, 1950, **15**, 82) have shown that such a mixture of isomers cannot be readily separated, even by repeated chromatography on very active alumina.

When the sesquiterpene was hydrogenated with palladized barium sulphate as catalyst, the hydrogen consumption ceased after 0·7 mol. had been consumed. This evidently represents the saturation of the methylene bond, for this partially reduced sesquiterpene gave neither formaldehyde nor formic acid on quantitative ozonolysis, but the yield of acetone was not significantly altered (0·27 mol.). The somewhat lower value for the methylenic determination by ozonolysis is probably due to the loss of small amounts of the rather volatile formaldehyde and formic acid.

The infra-red spectrum of metrosiderene shows a very strong band at 888 cm.$^{-1}$ which

is characteristic of the methylenic structure. There are no strong bands in the regions 780—810 and 1655—1685 cm.$^{-1}$, characteristic of the C–H deformation and double-bond stretching vibrations respectively, of a trisubstituted double bond in a cyclic olefin, *e.g.*, α-pinene. Furthermore there are no strong bands in the regions characteristic of the group –CH:CH– (Herout and Pliva, *Coll. Czech. Chem. Comm.*, 1949, **15**, 160). The second double bond is thus probably tetrasubstituted, *i.e.*, in position 1 : 9 or 9 : 10, as in formulæ (I—II) and (III—IV) respectively. This is also in agreement with the fact that only one double bond is readily hydrogenated, and that only a monohydrochloride can be prepared. Formulæ (III—IV) for metrosiderene are excluded since the ultra-violet spectrum of the sesquiterpene showed no absorption band.



(I) (II) (III) (IV)

Structures (I—II) representing metrosiderene have been confirmed by ozonolysis of the partially reduced (palladium) product. When the neutral product was oxidised with sodium hypoiodite, it gave iodoform, which must be derived from the methyl ketone formed by fission of the 1 : 9-double bond.

Experimental

(−)-*Metrosiderene.*—The sesquiterpenes from *M. umbellata* and from *D. biforme* were distilled separately through a Lecky and Ewell column (*Ind. Eng. Chem. Anal.*, 1940, **12**, 544) of 48 plates, and the distillate was collected in 3-c.c. portions. The fractions of *sesquiterpene* with the physical constants listed on p. 1179 were isolated (Found : C, 88·3; H, 11·7. $C_{15}H_{24}$ requires C, 88·2; H, 11·8%). To ensure that the fractions were homogeneous, the infra-red spectra of successive distillates were measured. The *nitrosate* was prepared by standard procedure in good yield, and had m. p. 122° after repeated crystallisation from chloroform–methanol (Found : C, 52·1; H, 6·8; N, 11·9%; *M*, by the micro-isopiestic method, 672, 680. $C_{30}H_{48}O_{12}N_6$ requires C, 52·6; H, 7·0; N, 12·3%; *M*, 684). The *monohydrochloride* was prepared by saturating a solution of the sesquiterpene in dry ether with hydrogen chloride : removal of the solvent gave a colourless liquid, n_D^{20} 1·5110, d_4^{20} 1·019 (Found : Cl, 15·22. $C_{15}H_{25}Cl$ requires Cl, 14·8%). No crystalline derivatives were obtained in attempted preparations of the nitrosochloride and nitrosite.

When a chloroform solution of perbenzoic acid and (−)-metrosiderene, $[\alpha]_D^{20}$ −8·05°, was kept at 0° until the iodine titre was constant, the oxygen absorption corresponded to 2·14 double bonds in the molecule. (−)-Metrosiderene, $[\alpha]_D^{20}$ −2·0°, gave an oxygen absorption corresponding to 1·90 double bonds.

Hydrogenation of (−)-*Metrosiderene.*—(*a*) A solution of (−)-metrosiderene (1·3 g.) in glacial acetic acid (30 c.c.) was shaken with hydrogen in the presence of Adams's catalyst (300 mg.) at atmospheric pressure. Hydrogen equivalent to 0·7 double bond was consumed in 10 min., and thereafter the rate rapidly diminished, and it ceased with the consumption of hydrogen equivalent to 1·85 double bonds after 4 hr. Distillation of the product over sodium gave *tetrahydrometrosiderene* (900 mg.), b. p. 134—135°/13 mm., n_D^{20} 1·4810, d_4^{20} 0·8920 (Found : C, 86·8; H, 13·1. $C_{15}H_{28}$ requires C, 86·5; H, 13·5%).

(*b*) (−)-Metrosiderene (4·2 g.) in ethanol (30 c.c.) was shaken with hydrogen in the presence of palladized barium sulphate. Hydrogen equivalent to 0·7 double bond was consumed before reduction ceased. Distillation of this product gave a fraction (A) (4·1 g.), b. p. 123—139°/13 mm.

Dehydrogenation of (−)-*Metrosiderene.*—(−)-Metrosiderene (4 g.) and finely powdered selenium (6 g.) were heated to 200° and the temperature then gradually raised to 280° and held there for 20 hr. Extraction with ether and distillation of the product yielded a blue liquid (3·2 g.), which was treated by Sherndal's method (*J. Amer. Chem. Soc.*, 1915, **37**, 167) for the isolation of azulene, but only a small quantity (50 mg.) was obtained. Distillation of the oil remaining from the azulene extraction gave two fractions, (*a*) b. p. 100°/3 mm., n_D^{20} 1·5100 (1·2 g. of unchanged oil), and (*b*) b. p. 115—122°/2 mm., n_D^{20} 1·5415 (1·7 g. of a colourless oil). Treatment of fraction (*b*) with saturated ethanolic picric acid gave a quantitative yield of cadalene picrate, m. p. and mixed m. p. 115° (from ethanol).

iso*Propylidene Determination.*—(−)-Metrosiderene, $[\alpha]_D^{20}$ −2·0° (117·9 mg.), was ozonised according to the method of Sorm *et al.* (*Coll. Czech. Chem. Comm.*, 1950, **15**, 92). Acetone (0·30 mol.) was found. A similar determination with (−)-metrosiderene of $[\alpha]_D^{20}$ −8·05° gave acetone (0·29 mol.).

Methylene Determination.—(−)-Metrosiderene, $[\alpha]_D^{20}$ −8·05° (117·5 mg.), was ozonised in carbon tetrachloride (30 c.c.), and the formaldehyde and formic acid were determined by the method of Sorm *et al.* (*loc. cit.*). Formaldehyde (0·29 mol.) and formic acid (0·22 mol.) were found. A similar series of determinations with (−)-metrosiderene of $[\alpha]_D^{20}$ −2·0° gave formaldehyde (0·30 mol.) and formic acid (0·28 mol.).

Ozonolysis of Partially Reduced (−)-Metrosiderene.—Ozonised oxygen was passed through a solution of partially reduced (−)-metrosiderene (A) (4·1 g.) in carbon tetrachloride (50 c.c.) for 6 hr. The viscous ozonide was decomposed by refluxing distilled water (150 c.c.) in 30 min., and the mixture was then steam-distilled to give 250 c.c. of distillate. Acetone, identified as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 124—125°, was identified in this distillate. The neutral (2·5 g.) and the acid (1·0 g.) fraction from the ozonolysis were isolated in the usual manner. Oxidation of the neutral fraction (70 mg.) with sodium hypoiodite gave iodoform, m. p. and mixed m. p. 118°.

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*Lanthanon Complexes with Ethylenediaminetetra-acetic Acid. Part IV.**

By R. C. VICKERY.

[Reprint Order No. 4613.]

The displacement of lanthanons from anionic complexes with ethylenediaminetetra-acetic acid (H_4enta) by added cationic lanthanons has been studied spectrophotometrically. The displacement proceeds in order of decreasing atomic number and stability constant of the lanthanon complex; *i.e.*, the cation of a lanthanon of higher atomic number and higher stability constant will displace from anionic "enta" complex a lanthanon of lower atomic number and lower stability constant.

This principle of displacement has been applied to lanthanon separation, pure [Ln enta]$^-$ complexes being progressively converted into cationic form by the addition of calculated quantities of cationic lanthanon. The lanthanon displaced from anionic complex is then extracted from solution by a cation-exchange resin. Good separations of many of the lanthanons have thus been achieved although the pairs praseodymium–neodymium and dysprosium–holmium and the triad samarium–europium–gadolinium remain recalcitrant. Lanthanum, samarium, thulium, ytterbium, and lutetium are readily prepared in good purity by this technique, and satisfactory concentrations of terbium and dysprosium are readily achieved.

ALL the lanthanons form with ethylenediaminetetra-acetic acid (H_4enta) anionic complexes of the type [Ln enta]$^-$. In spite of the comparatively narrow range of the overall stability constant values for these complexes (log $\bar{K}_{La}$ 15·3, log $\bar{K}_{Yb}$ 18·7; Part III *), attempts have been made to use the differences in stability of the individual complexes as a basis for improved method of lanthanon separation. Except, however, in the isolated instances of lanthanum (Vickery, *J.*, 1951, 1817), praseodymium and neodymium (*idem*, *J.*, 1952, 4357), and in the gross separation of light and heavy lanthanons (Marsh, *J.*, 1951, 3057; 1952, 4804), only mediocre separations have been achieved although even these have shown many improvements upon classical methods of lanthanon fractionation.

* Part III, *J.*, 1952, 1895.

The formation of anionic lanthanon complexes exerts a profound effect upon the absorption spectra of the coloured lanthanons (Vickery, Part II, *J.*, 1952, 421), consisting of a splitting of the absorption bands and a considerable increase in their extinction coefficients. Exchange of lanthanons between anionic and cationic forms has therefore been studied by noting the effect on extinction coefficients of the absorption spectra of enta-complexed lanthanons by the addition of other lanthanons in cationic form. Figs. 1 and 2 show the progress of such exchanges with increasing quantities of added lanthanon cations, although the materials upon which the experiments are based were not necessarily in equilibrium. One of the more significant features of these figures lies in the further evidence they give of the formation only of complexes at 1 : 1 molar ratios of Ln : enta. No diminution of extinction coefficient occurs until an equivalent of cationic lanthanon is present, whereupon a sharp fall is observed to the usual value of the extinction coefficient of the cationic lanthanon initially present in anionic complex (Fig. 1). If two coloured lanthanons are present in the same system *e.g.*, $[Pr\ enta]^- + Nd^{3+}$, the spectra of complexed praseodymium and simple neodymium ions coexist (Fig. 2) until sufficient neodymium is present fully to displace the praseodymium from the enta complex. Then the nature of the spectra is reversed and the picture is one of complex neodymium and simple praseodymium ions. If a complex of any ratio other than 1 : 1 existed, the variation in

FIG. 1.

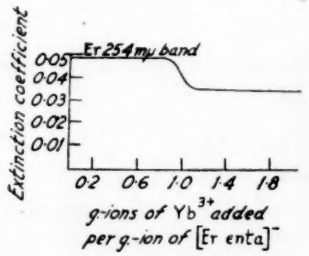
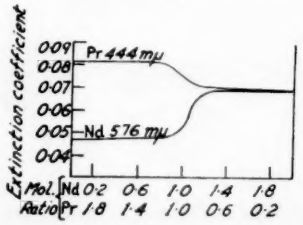


FIG. 2.



extinction coefficient and nature of the spectra would be a more gradual one and discontinuities would be expected in the extinction coefficient graphs at ratios of Ln : enta corresponding to the formation of different complexes.

The abrupt fall in extinction coefficient indicates also that the rate of exchange is quite rapid. Further measurements showed that the exchange reaction

$$[Ln_A\ enta]^- + Ln_B^{3+} \longrightarrow Ln_A^{3+} + [Ln_B\ enta]^-$$

proceeds according to the relative stabilities of the Ln_A and Ln_B complexes, *i.e.*, at a rate determined by $\log \bar{K}(Ln_B)/\log \bar{K}(Ln_A)$, becoming infinitely fast when Ln_B = ytterbium and Ln_A = lanthanum.

This exchange of anionic and cationic lanthanon forms postulates the rule that the displacement series is that of decreasing atomic number, *i.e., the cation of a lanthanon of higher atomic number will displace from anionic complex a lanthanon of lower atomic number.* The anionic and cationic mixture then resulting can easily be separated by treatment with an ion-exchange resin.

On this displacement and resolution of ionic forms has been founded a method of lanthanon separation. Consider the system $[(\frac{1}{3}Pr, \frac{1}{3}Nd, \frac{1}{3}Sm)(enta)]^-$. If, to the solution of such a system be added an additional $(\frac{1}{3}Nd^{3+})$, *i.e.*, an equivalent of the praseodymium content, the following exchange may be considered to take place :

$$[(\tfrac{1}{3}Pr, \tfrac{1}{3}Nd, \tfrac{1}{3}Sm)(enta)]^- + (\tfrac{1}{3}Nd^{3+}) \longrightarrow [(\tfrac{2}{3}Nd, \tfrac{1}{3}Sm)(enta)]^- + (\tfrac{1}{3}Pr^{3+})$$

and the cationic praseodymium can readily be removed from the system by passage through a cation-exchange resin or by batch-wise extraction with such a resin.

Marsh (*loc. cit.*) introduced a technique of lanthanon separation by fractionally precipitating the lanthanons as alkali double sulphates in the presence of enta. The

efficacy of this technique depends upon the partition of lanthanons between their simple cationic forms and their anionic, enta, complexes, the cationic fraction being progressively precipitated by sodium sulphate.

This present mode of separation could of course be applied to lanthanon mixtures in bulk, but is limited by the requirement of increasing quantities of lanthanons with increasing stability of the complexes, and this increase roughly parallels the increase in rarity. Thus, in a complete separation of all the lanthanons by this system, sufficient lutetium would have to be available to displace all the preceding lanthanons. With most of the heavy lanthanons available only in little more than gram quantities, this technique therefore has been applied only to more conservative systems in which the component lanthanons have undergone a certain prior degree of fractionation and concentration. The preliminary requirements of this technique are: (i) accurate determination of the composition of the mixture to be resolved, (ii) preparation of the pure enta complex of the mixture so that no extra-complexing effects occur owing to the presence of excess of enta, (iii) the use of dilute solutions, (iv) the use of ion-exchange resins in the sodium form. The necessity of this last requisite is clear when it is realised that hydrogen resins will decrease the pH of the anionic lanthanon solution with consequent disruption of the complexes. On the other hand, the increasing sodium chloride content of the solutions must introduce variations in the stability constants of the lanthanon–enta complexes (cf. Martell *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 5745; *J. Phys. Chem.*, 1952, **56**, 993) and this may be one of the side reactions which prevent the exchange and separation being 100% effective. Replacement of the sodium resin by one in the potassium or ammonium form has an even greater adverse effect on the separations achieved.

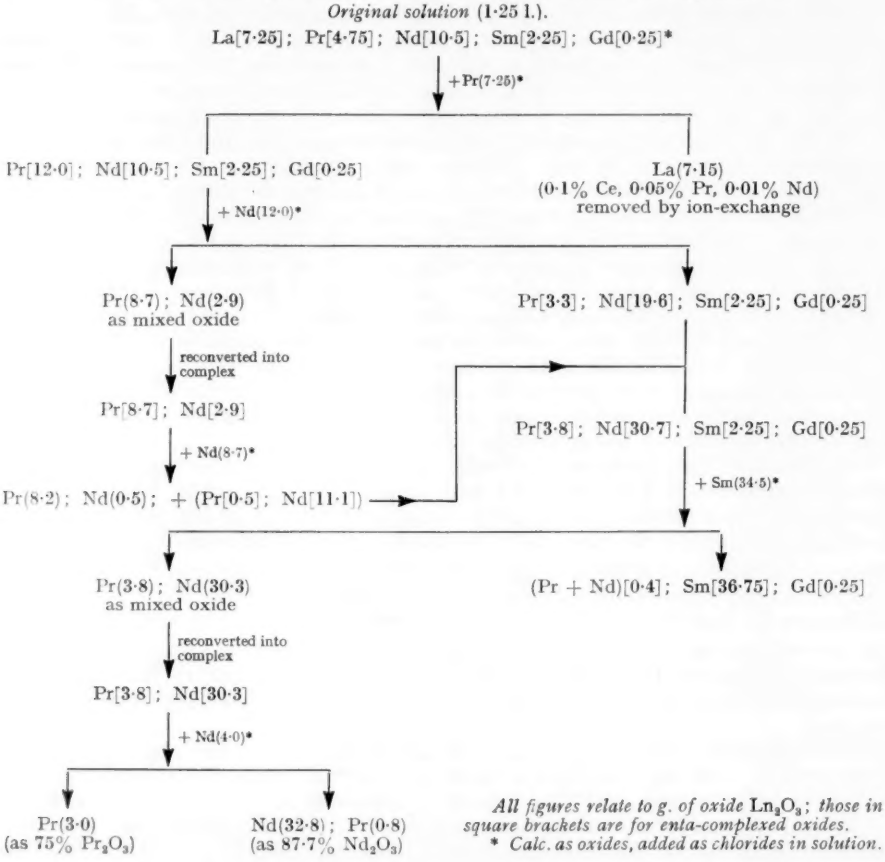
Separation of Light Lanthanons.—From a mixture of light lanthanons, lanthanum can easily be removed in high yield and purity (see Table 1); indeed, by virtue of its significantly lower tendency to complex formation than any of the other lanthanons, lanthanum is probably the most easily separated of all the lanthanons by this technique. There is a difference of 0·75 log $\bar{K}$ unit between the stability constants of lanthanum and cerium enta complexes—a much greater difference than between any other two consecutive lanthanons (average difference, *ca.* 0·30 unit). With cerium removed from the system by the conventional oxidation–hydrolysis procedures, this difference becomes 1·25 log $\bar{K}$ units (between lanthanum and praseodymium), increasing immeasurably the ease with which displacement of lanthanum from anionic complex and its subsequent removal can be effected.

The mutual separation of praseodymium and neodymium by this exchange technique is incomplete. The enta complexes of these two elements differ in their stability constant values by only 0·2 unit, and this appears to approach the limit of resolution by this technique. Part of the difficulty encountered in separating this pair may lie in the degree to which each affects the spectrophotometric determination of the other. Analytical error, however, cannot wholly account for the lack of complete discrimination between neodymium and praseodymium. It will introduce inaccuracy in the quantity of cationic neodymium required to displace the anionic praseodymium, but the contamination of praseodymium by neodymium and *vice versa* is not a fractional effect. No better separation is achieved when cationic neodymium is added fractionally to the system. However, the 3—4-fold increase in praseodymium concentration in one operation, and 4—5-fold increase in two, is not insignificant (see Table 1).

Interpolation of manganese between praseodymium and neodymium was a notable feature of previously reported ion-exchange separations (*loc. cit.*), but this separating effect was not manifest in the exchange system now studied. Addition of Mn^{2+} to the system even in excessive quantities produced no disintegration of the $[Pr\ enta]^-$ complex. It was quite evident that the present system was not to be compared with those previously studied in which the exchange resin played a dynamic part in the separation as distinct from its now more passive role of collector. Although it had been shown (Vickery, *Nature*, 1952, **170**, 665) that elution series, *i.e.*, complex degradation series, could vary according to the ratio of bi- to ter-valent ions, it was still not possible in this system to interpolate any element between praseodymium and neodymium.

An intensive study of the neodymium–samarium separation was unnecessary because of the excellent reduction methods available for the separation and purification of samarium. Since, however, there is a minimum concentration of samarium below which

TABLE 1. *Displacement separation of light lanthanon complexes.*



All figures relate to g. of oxide Ln_2O_3; *those in square brackets are for enta-complexed oxides.*
* *Calc. as oxides, added as chlorides in solution.*

reduction techniques are relatively inefficient (Vickery, "The Chemistry of the Lanthanons," Butterworth. London, 1953), determination of the extent of samarium separation was important. With 0·45 unit difference in the stability constants of neodymium enta and samarium enta complexes an appreciable degree of separation might be expected by the displacement technique, although an efficiency as high as that of the lanthanum–praseodymium separation would be unlikely. The confirmation obtained of this is shown in Table 1. Separation of neodymium (plus residual praseodymium) from the heavier lanthanons may be considered complete in three fractionations, and concentration of samarium to that adequate for reduction purposes, in one operation.

Separation of "Middle" Lanthanons.—The term "middle" lanthanons is retained from older nomenclature to indicate samarium, europium, gadolinium, terbium, and dysprosium. The first three have proved most difficult to separate by ion-exchange techniques (*e.g.*, Ketelle and Boyd, *J. Amer. Chem. Soc.*, 1947, **69**, 2811) and the apparent identity of the stabilities of samarium– and gadolinium–enta complexes—$\log K_{SmGd} = 17·2$—did not augur well for the application of the displacement technique to the separation of this triad. The reduction methods available for separation and purification of samarium

and europium rendered a close study of the samarium–europium–gadolinium system superfluous and it was immediately obvious that no separation of this triad was likely to be achieved by the displacement technique.

Insufficient terbium and dysprosium were available to study the disruption of gadolinium and terbium complexes, so the effect of fractional addition of Y^{3+} was examined. The stability constant of the yttrium–enta complex is 18·0, placing the element at about the position of holmium in the lanthanon series. Yttrium should therefore displace (samarium–europium–gadolinium), terbium, and dysprosium from solution *en bloc*. The extent to which this gross displacement can be converted into a fractional one is seen in Table 2. No separation of the samarium–europium–gadolinium triad is evident, but

TABLE 2. *Displacement separation of middle lanthanon complexes.*

Initial solution : 1 l. containing [4·0 g. Sm, 0·6 g. Eu, 10·0 g. Gd, 0·8 g. Tb, 2·0 g. Dy, 0·2 g. (max.) Ho, 2·4 g. Y].*

17·6 g. of Y_2O_3 (as chloride solution) added fractionally. Fractions 1—7, 9—13 were cationic extracts, fractions 8 and 14 were anionic eluates.

Fr.	1	2	3	4	5	6	7	8
Wt., g.	3·80	3·80	3·32	2·44	2·15	2·07	2·07	17·7
Sm, %	37·4	27·6	23·0	19·3	8·8	4·35	2·42	—
Eu, %	8·43	4·75	2·4	0·41	—	—	—	—
Gd, %	54·0	65·3	65·5	59·5	43·5	20·8	10·2	0·85
Tb, %	0·25	2·1	5·1	9·85	8·8	4·35	1·00	—
Dy, %	—	—	—	0·41	4·16	11·6	20·5	7·00
Ho, %	—	—	—	—	0·45	0·97	1·00	0·62
Y, %	—	0·25	4·0	10·83	34·29	57·93	64·88	91·53

Frs. 4—8 re-" complexed " and treated serially with YCl_3 (75% theoretical requirement).

Y_2O_3 added, g.			Wt., g.	Sm, %	Eu, %	Gd, %	Tb, %	Dy, %	Ho, %	Y, %
1·63	→ Fr. 4 →	Fr. 9	1·74	25·8	0·6	63·2	10·7	—	—	—
	↓ Fr. 5									
1·40	→	Fr. 10	1·50	11·3	—	76·5	12·0	—	—	—
	↓ Fr. 6									
0·91	→	Fr. 11	0·88	11·4	—	62·5	15·9	10·2	—	—
	↓ Fr. 7									
0·71	→	Fr. 12	0·68	8·8	—	33·8	6·9	50·0	1·5	—
	↓ Fr. 8									
1·40	→	Fr. 13	1·71	—	—	8·8	—	80·1	4·1	7·0
	↳	Fr. 14	26·0	—	—	—	—	0·8	0·3	98·9

* Unless otherwise indicated, figures given are in terms of "Ln_2O_3;" Y_2O_3 was determined by difference.

some concentration of terbium occurs in the middle of the eight fractions made. Dysprosium is clearly concentrated at the tail of the series. A second row of fractionations on Fraction 4—8 greatly increased the terbium concentration and doubled the dysprosium concentration.

No stability constant has been determined for the [Tb enta]$^-$ complex but since the separation of terbium–dysprosium is apparently more easily achieved than that of praseodymium–neodymium (see p. 1182), the difference in log $\bar{K}$ values between the terbium and dysprosium complexes must be somewhat greater than 0·2 unit. Similarly, to account for the greater separation of terbium from dysprosium than from gadolinium, the stability

constant for the terbium complex must be closer to the value for the gadolinium complex (17·2) than to that of the dysprosium complex (17·75). The evidence therefore indicates the [Tb enta]$^-$ complex to have a stability constant value between 17·4 and 17·6 log $\bar{K}$ units.

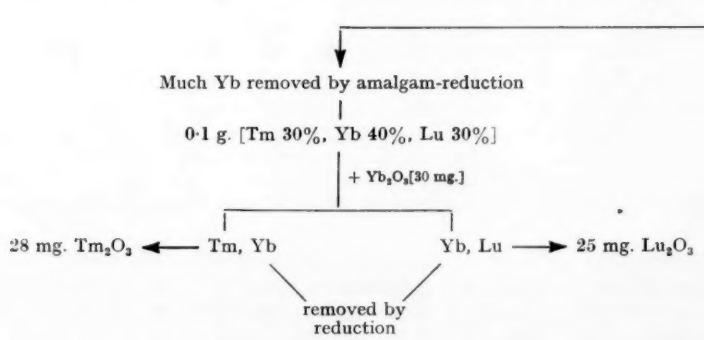
Separation of Heavy Lanthanons.—The heavy lanthanon mixture used contained insufficient holmium, thulium, or lutetium for their reported separations to have much significance. One feature of especial interest, however, was the possible separation of yttrium and erbium; the complexes of these elements differ only by 0·15 unit in their stability constant values so that little if any separation of these two elements could be expected by this displacement technique. Preferential disruption of the yttrium complex by the addition of erbium cations certainly did not effect any noticeable separation, and the fractional addition of Yb^{3+} did not give very different results (Table 3). In the double row of fractionations made, a noticeable feature is the concentration of holmium (and residual dysprosium) at the head of the series with yttrium interpolated between holmium and erbium. This indicates that the stability constant value for the [Ho enta]$^-$ complex lies between 18·0 and 17·75. Because of this, little differentiation can be expected between dysprosium and holmium. This fractional disruption of the complexes with cationic ytterbium gave some separation of yttrium and erbium but was not so effective as separation by ferricyanide precipitation. The separation of erbium from ytterbium is achieved without difficulty (0·55 unit difference in log $\bar{K}$ values). The tendency for the small amount of thulium present to remain with the ytterbium indicated that the stability of the [Tm enta]$^-$ complex is closer to that of the ytterbium than of the erbium complex.

TABLE 3. *Displacement separation of heavy lanthanon complexes.*

Initial solution: 500 ml. containing [0·9 g. Dy, 0·1 g. Ho, 2·9 g. Y, 3·8 g. Er, 0·05 g. Tm, 2·2 g. Yb, 0·05 g. Lu].

The sequence employed was that outlined in Table 2. In the first row of the series 7 g. of Yb_2O_3 as chloride were added fractionally to the initial solution to give 8 fractions (1—7 cationic, 8 anionic). These were re-complexed and each fraction again treated with $YbCl_3$. For convenience, analyses of the first row are omitted.

	9	10	11	12	13	14	15	16	17
Wt., g.	0·65	0·91	1·42	1·61	1·86	1·91	1·97	1·92	11·86
Dy, %	80·0	58·0	17·0	9·4	3·0	—	—	—	—
Ho, %	8·5	8·0	3·0	0·5	—	—	—	—	—
Y, %	8·5	24·0	57·0	58·6	40·1	24·5	9·3	3·7	—
Er, %	3·0	10·0	23·0	31·5	41·4	27·2	11·0	4·1	—
Tm, %	—	—	—	—	—	—	0·5	0·5	0·25
Yb, %	—	—	—	—	15·5	45·5	78·7	91·2	99·50
Lu, %	—	—	—	—	—	—	0·5	0·5	0·25



No lutetium being available for the study of the displacement of thulium or ytterbium complexes, the removal of ytterbium from these heaviest lanthanons was effected by the amalgam reduction technique, leaving a small quantity of a thulium–lutetium concentrate. This was converted into the anionic enta complex, and sufficient Yb^{3+} again added to displace the thulium. Complete separation of thulium from lutetium was thus obtained,

the thulium being concentrated some 5—6 fold in the cationic fraction with some ytterbium. Ytterbium being again removed from the thulium–ytterbium and ytterbium–lutetium fractions by reduction, small amounts of thulium and lutetium of good purity were obtained.

Experimental

The mixed lanthanon oxides used had accrued from previous separations of lanthanons derived from monazite (N.S.W.) and davidite (S.A.). These oxides had previously undergone differentiation by fractional crystallisation or basicity techniques and, to some extent, by crude ion-exchange fractionation. Their constitution, and those of the fractions obtained, were determined spectrophotometrically by means of the Beckman DU instrument utilising the extinction coefficients, etc., given by Moeller and Brantley (*Analyt. Chem.*, 1950, **22**, 433) and Wylie (*J. Soc. Chem. Ind.*, 1950, **69**, 143). Terbium was determined by the " active oxygen " method (Barthauer and Pearce, *Ind. Eng. Chem. Anal.*, 1946, **18**, 479).

The individual lanthanon oxides (of neodymium, praseodymium, samarium, erbium, etc.) were all of high purity (*ca.* 99·8%) and had been extracted and purified from the above sources by conventional methods and ion-exchange techniques. Again, all spectrophotometric studies on the displacement of anionic complexes by cations were conducted by use of the Beckman DU instrument. Throughout this study, the spectrophotometric evidence of complex displacement, and the inability of the separation technique to differentiate between complexes differing by less than *ca.* 0·2 unit in stability-constant values, were noteworthy. Much of this must be attributable to the limit of selectivity of the resin. Some degree of anionic take-up always occurs with cationic resins and *vice versa*.

The successful operation of this mode of separation depends upon two features: correct preparation of the initial complex, and correct preliminary treatment of the exchange resin. The avoidance of excess of enta, or the presence of sodium enta in the initial complex is essential. Consider the system: $[(\frac{1}{3}Pr, \frac{1}{3}Nd, \frac{1}{3}Sm)(enta)]^- + Na_4(enta) + (\frac{1}{3}Nd^{3+})$. It is clear that interaction of the sodium enta and the neodymium cations will occur preferentially to the displacement of praseodymium from the complex, or, if the cationic neodymium *did* displace praseodymium from its anionic complex, the liberated Pr^{3+} would form a complex with the excess of sodium enta and not be removed by the exchange resin. The use of a gross excess of cationic neodymium could overcome this " extra " complexing effect but, unless the excess of sodium enta were accurately known and corrected for, this excess of neodymium would be extracted together with the liberated praseodymium and thus afford little or no separation of the lanthanons. In the preparation of the complexes used in this study care was always taken to employ a slight excess of lanthanon oxide and slight deficiency of sodium hydroxide, otherwise the method was that of Marsh (*loc. cit.*). The solution of the complex was evaporated to as small a bulk as possible before crystallisation in order to minimise the volume of mother-liquor and to reduce the separation which would occur by fractional crystallisation of the complex. The solid salt prepared was filtered off, washed once with ice-water, and dried by suction, a portion of the solid then being taken for complete analysis of its lanthanon content, to check the composition of the complex and to provide for displacement by the correct quantity of cationic lanthanon.

Correct appreciation of the function of the resin is also necessary. Data given by Duncan and Lister (*Quart. Reviews*, 1948, **2**, 307) give the maximum capacity of Dowex 50 resin as 4·92 m.-equiv./g. of dry resin, *i.e.*, 0·046 g. of La_2O_3 or 0·058 g. of Yb_2O_3 will saturate 1 g. of dry resin. We have found this maximum capacity to decrease with increasing pH, and the figures now obtained are somewhat higher than those given by these workers (0·075 g. La_2O_3, 0·086 g. Yb_2O_3 at pH 1·4; 0·052 g. La_2O_3, 0·066 g. Yb_2O_3 at pH 6·6). In order to avoid take up of oppositely charged ions by the resin, it is probably preferable to convert into cationic form rather more anionic lanthanon than can be held by the amount of resin taken, but this must be considered in the light of the degree of separation desired, since any cationic lanthanon remaining unextracted will adulterate the following fraction and nullify to an increasing extent the displacement achieved.

In the separations recorded here, 25-g. amounts of resin were considered to take up 1·5—2·0 g. of Ln_2O_3. The time necessary for this take-up is also of importance: equilibrium should be established as closely as possible; with the light lanthanons shaking for as long as 12 hr. at room temperature has been necessary, but the heavier lanthanons attain equilibrium more readily, *ca.* 30 min. being sometimes sufficient.

Complete conversion of the resin into its sodium form must be ensured. Lack of attention to this will leave hydrogen ions on the resin and these, on displacement by Ln^{3+}, will reduce the pH of the complex solution with resultant partial disruption of the complex and precipitation of H_4enta. The complex solution should have a pH of 6·8—7·2 and the added lanthanon chloride solution should approach as near to neutrality as possible.

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The Bodroux Reaction.

By H. LL. BASSETT and C. R. THOMAS.

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For the reaction between an aminomagnesium halide and a simple ester, yielding a substituted amide, the mechanism proposed by Bodroux (*Bull. Soc. chim.*, 1905, **33**, 831), involving two molecules of aminomagnesium halide and one molecule of ester in an intermediate complex, has been shown to be incorrect. The complex contains equimolecular proportions of the halide and the ester, the second molecule of aminomagnesium halide acting by decomposing the complex.

AN aminomagnesium halide, formed when a primary or secondary amine reacts with a Grignard reagent at room temperature, reacts with a simple aliphatic or aromatic ester to yield a substituted amide.

The reaction has been described by Bodroux (*Bull. Soc. chim.*, 1905, **33**, 831; 1906, **35**, 519; 1907, **1**, 912; *Compt. rend.*, 1904, **138**, 1427; 1905, **140**, 1108; 1906, **142**, 401). He postulated the formation of an intermediate compound involving two molecules of the aminomagnesium halide and one of the ester, because the yield of amide was never more than 50% (based on the ester) when equimolecular quantities of ester and aminomagnesium halide were used, although use of double the quantity of aminomagnesium halide gave an almost theoretical yield.

In this way, with two equivs. of aminomagnesium halide, hexanoanilide, dodecanoanilide and -*m*-toluidide, and *NN*-diphenyl-acetamide and -benzamide have now been prepared in almost theoretical yield (based on the ester).

If Bodroux's mechanism is correct, by using *o*-phenylenediamine as the amine, an intermediate compound should be produced involving the two adjacent groups of the *o*-phenylenebisaminomagnesium dihalide with the ester, and this should give a stable 2-substituted benziminazole as the end-product. No trace of 2-methyl- or 2-phenylbenziminazole was obtained when *o*-phenylenebisaminomagnesium di-iodide was treated with methyl acetate or benzoate respectively, even when more vigorous conditions than usual were used.

Isolation of compounds of type (I) postulated by Bodroux (*loc. cit.*) as intermediates has not been described. However, it has now been found that equimolecular proportions of

(I) $IMg{\cdot}O{\cdot}CPh(NHPh)_2$ $IMg{\cdot}O{\cdot}CPh(OMe){\cdot}NHPh$ (II)

anilinomagnesium iodide and methyl benzoate give a stable white powder, shown by analysis to be (II). Decomposition of this with dilute acid gave a yield of 32% of benzanilide, whereas refluxing the addition compound with an equimolecular quantity of anilinomagnesium iodide in ether for one hour gave 87% of benzanilide. This compound (II), formed from equimolecular quantities of anilinomagnesium iodide and methyl benzoate, also gave a high yield (96%) of pure benzanilide (free from *NN*-diphenylbenzamide) when refluxed with an equimolecular proportion of diphenylaminomagnesium iodide (prepared from diphenylamine and methylmagnesium iodide). In a similar manner the addition compound formed between equimolecular quantities of diphenylaminomagnesium iodide and methyl benzoate gave a high yield (89%) of pure *NN*-diphenylbenzamide (free from benzanilide) when refluxed with an equimolecular proportion of anilinomagnesium iodide.

These experiments showed that the second equivalent of aminomagnesium halide does not enter into complex formation, as suggested by Bodroux, but acts by decomposing the addition compound.

Pure *NN*-diphenylbenzamide was also obtained when the diphenylaminomagnesium iodide–methyl benzoate addition compound was allowed to react with aniline (86% yield) and with aqueous sodium hydroxide solution (60% yield).

It thus appears that the reaction between aminomagnesium halides and esters proceeds through an addition compound involving equimolecular quantities of the reactants, and that this addition compound can be broken down by basic reagents to give almost quantitative yields of a substituted amide, although decomposition by acidic reagents gives a much smaller yield of the same compound.

Experimental

The Grignard reagent used in all cases was methylmagnesium iodide, and the aminomagnesium iodides were prepared and used *in situ*. All ethereal extracts were dried over anhydrous potassium carbonate.

General Method.—The amine (0·1 mole) in dry ether (30 ml.) was added slowly to methylmagnesium iodide (0·1 mole) in dry ether (50 ml.). After the vigorous reaction had subsided, the ester (0·05 mole) in ether (*ca.* 20 ml.) was added, and the mixture refluxed on a warm water-bath for 2 hr. It was then decomposed by cautious addition of water (50 ml.), followed by sufficient 2N-hydrochloric acid to dissolve basic magnesium compounds. The separated ethereal extract was dried, and the ether and unchanged amine were distilled off. The residue, when cooled, set to a mass of crystals which were recrystallised.

In this manner the following were prepared: hexanoanilide (from anilinomagnesium iodide and methyl hexanoate), m. p. 52—53° (87%); dodecano-anilide, m. p. 76—77° (80%), and -*m*-toluidide, m. p. 59—60° (89%) (Bowen and Smith, *J. Amer. Chem. Soc.*, 1940, **62**, 3522, give 54—56° as m. p. of this compound), *NN*-diphenyl-acetamide, m. p. 95—98° (85%), and -benzamide, m. p. 178—179° (88%).

Reactions with o-*Phenylenebisaminomagnesium Di-iodide.*—(*a*) The filtered Grignard reagent (0·05 mole) was added dropwise to *o*-phenylenediamine (2·7 g., 0·025 mole) in ether (100 ml.), and then methyl acetate (1·9 g., 0·025 mole) in ether (10 ml.). The mixture was refluxed with stirring for 2 hr., decomposed with water and dilute acid, and worked up as described above. A residue (2·3 g.) was obtained, which crystallised from hot water as brownish plates, m. p. 100—102° (*o*-phenylenediamine, m. p. 102°; 2-methylbenziminazole, m. p. 176°), and were thus unchanged *o*-phenylenediamine.

(*b*) A large excess of methyl acetate (9·3 g., 0·125 mole) was used, and refluxing with stirring continued for 4 hr. Otherwise the experiment was carried out as in (*a*), and the amine recovered (2·3 g., 85%) had m. p. 101—102°.

(*c*) A mixture of *o*-phenylenediamine (2·7 g., 0·025 mole) and methyl benzoate (17·0 g., 0·125 mole) in ether (100 ml.) was added dropwise to the Grignard reagent (0·025 mole), and the mixture refluxed for 4 hr. with stirring. After decomposition and drying of the ethereal layer, this was distilled, giving methyl benzoate (15·8 g., 93%) at 190—200°, and *o*-phenylenediamine (2·3 g., 85%), m. p. 100—102° (2-phenylbenziminazole has m. p. 288°).

The Addition Compound.—A mixture of aniline (9·3 g., 0·1 mole) and methyl benzoate (13·6 g., 0·1 mole) in ether (30 ml.) was added dropwise to methylmagnesium iodide (0·1 mole). The mixture was then filtered through a Büchner funnel, a viscous material being retained on the filter. This was rapidly transferred to a vacuum-desiccator, and dried over concentrated sulphuric acid at 2 mm. After 12 hr., it had changed to a white powder. About 0·5 g. was acidified with dilute nitric acid, the precipitated benzanilide filtered off, and the iodide in the filtrate determined as silver iodide [Found: N, 3·7; I, 33·9. Calc. for $C_{19}H_{17}ON_2MgI$ (I): N, 6·4; I, 28·8. $C_{14}H_{14}O_2NMgI$ (II) requires N, 3·7; I, 33·5%].

Reactions of the Addition Compound.—(a) *With dilute acid.* The residue of benzanilide from the previous experiment represented a yield of 32%, and had m. p. 161—162° (lit., m. p. 162°).

(b) *With anilinomagnesium iodide.* This reagent (0·025 mole) was prepared in ether, and the addition compound (9·5 g., 0·025 mole) added. The mixture was refluxed for 1 hr. with stirring, and decomposed with dilute hydrochloric acid. Benzanilide (4·3 g., 87% based on the addition compound) was obtained, having m. p. 162° after one crystallisation from aqueous ethanol.

(c) *With diphenylaminomagnesium iodide.* The addition compound (0·025 mole) was added

to diphenylaminomagnesium iodide (0·025 mole) in ether, and the reaction carried out as in (b), giving benzanilide (4·7 g., 96% based on the addition compound), m. p. and mixed m. p. 162—163° after one crystallisation from aqueous ethanol.

(d) *Action of anilinomagnesium iodide on the diphenylaminomagnesium iodide–methyl benzoate addition compound.* The addition compound was prepared *in situ* from equimolecular quantities (0·025 mole) of the reagents, and to it was added anilinomagnesium iodide (0·025 mole). The product, worked up as in (*b*), proved to be *NN*-diphenylbenzamide (6·0 g., 89% based on the weight of ester, and hence of addition compound), m. p. and mixed m. p. 178—178·5° after one crystallisation from aqueous ethanol (lit., m. p. 177°, 179°).

(e) *Action of aniline on the addition compound, as in* (d). The addition compound (0·025 mole) was prepared *in situ*, and an equimolecular proportion of aniline added to it. The reaction was then carried out as in (b), and the product shown to be *NN*-diphenylbenzamide (5·8 g., 86%), m. p. and mixed m. p. 178—178·5° after one crystallisation from aqueous ethanol.

(f) *Action of sodium hydroxide on the addition compound, as in* (d). To the addition compound (0·025 mole, *in situ*) was added 10% aqueous sodium hydroxide (10 ml.). After 1 hr.' refluxing with stirring and decomposition with dilute hydrochloric acid, *NN*-diphenylbenzamide (4·1 g., 60%) was obtained, having m. p. and mixed m. p. 178—178·5° after one crystallisation from ethanol.

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Nucleophilic Displacement Reactions in Aromatic Systems. Part III. Kinetics of the Reactions of Chloronitropyridines and Chloropyrimidines with Piperidine, Morpholine, Pyridine, and Aniline.*

By N. B. CHAPMAN and C. W. REES.

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Arrhenius parameters for the reactions in ethanol of piperidine and of morpholine with 2-chloro-, 2-chloro-4-methyl-, 2-chloro-4 : 6-dimethyl-, 4-chloro-6-methyl-, and 4-chloro-2-methyl-pyrimidine are presented, and similar values for the reactions of piperidine with 2-chloro-3-nitro-, 2-chloro-5-nitro-, and 2-chloro-4-methyl-5-nitro-pyridine. The rate-diminishing influence of nuclear methyl groups *meta* to the seat of substitution is briefly discussed although the major influence is on the value of A, rather than of E. In reactions of a structurally analogous nitropyridine derivative, the methyl group also influences Arrhenius parameters by steric inhibition of NO_2–ring conjugation. Nucleophilic displacement of chlorine from the 4-position in the pyrimidine ring is associated with an energy of activation of ~2000 cal. less than that for the 2-position, and E and log A for reactions of the inaccessible 4-chloropyrimidine are estimated at ~10,500 cal. and 5·0 respectively. The effect of a second *ortho*-cyclic nitrogen atom on E for nucleophilic displacement is estimated as a diminution of ~7500 cal. The reactivity of 2- and 4-chloropyrimidine derivatives is also compared in terms of Arrhenius parameters with that of each of a series of analogous nitro-compounds. The results are discussed in structural terms. Evidence of autocatalysis by formed acid in the reactions of chloropyrimidines with aniline, *p*-toluidine, and pyridine is provided. It is also shown that ion exchange with the solvent is unimportant in these reactions.

PARTS I and II of this series (*J.*, 1952, 437; 1953, 3392) were concerned mainly with the reactions of chloronitropyridines. The present communication records an extension of the investigation into the pyrimidine series. Neither primary aromatic amines nor pyridine showed regular kinetics in reactions with chloropyrimidines (see p. 1193). With piperidine

* Part II, *J.*, 1953, 3392.

and morpholine, however, we observed a series of second-order reactions in ethanol with various chloropyrimidines. In contrast to 2-chloropyrimidine, 4-chloropyrimidine is very difficult to prepare in quantity, and very unstable, and would almost certainly undergo solvolysis under our conditions. To study the displacement of chlorine from the 4-position in the pyrimidine nucleus we have been obliged, therefore, to utilise 4-chloro-2- and -6-methylpyrimidine. By including 2-chloro-4-methyl- and -4 : 6-dimethyl-pyrimidine we have been able to elucidate the influence of nuclear methyl groups on the reactivity of chloropyrimidines. These changes in the type of system studied made desirable a study of the kinetics of the reactions in ethanol of 2-chloro-3-nitro-, 2-chloro-5-nitro-, and 2-chloro-4-methyl-5-nitro-pyridine with piperidine, for comparison. The last chloro-compound, formerly unknown, was prepared from the available 2-amino-4-methylpyridine by a method very similar to that used for 2-chloro-5-nitropyridine (Part I, p. 438).

The mobility of halogens towards nucleophilic reagents in the 2- and 4-positions in the pyrimidine and quinazoline rings is well known in preparative work (cf. Lythgoe, *Quart. Reviews*, 1949, **3**, 181), and the instability of 4-chloropyrimidine testifies to the greater reactivity at the 4-position. However, there has been no previous kinetic work in this field, and there are very few qualitative and semiquantitative investigations on record. Andrisano and Modena (*Gazzetta*, 1951, **81**, 398) and Banks (*J. Amer. Chem. Soc.*, 1944, **66**, 1127) have studied the reactivity of more highly substituted chloropyrimidines than the simple compounds under discussion, and Banks has emphasised the influence of protons as catalysts in these reactions, a circumstance largely responsible for our choice of nucleophilic reagent. We return to this point in the discussion.

The present paper and its predecessors go some way towards achieving our original object, *viz.*, the provision of experimental results linking the kinetics of nucleophilic substitution in the benzene, pyridine, and pyrimidine series.

Experimental

Materials.—Chloro-compounds. 4-Chloro-6-methylpyrimidine was prepared by desulphurisation of 6-methyl-2-thiouracil by Williams, Ruehle, and Finkelstein's method (*J. Amer. Chem. Soc.*, 1937, **59**, 528), followed by treatment of the crude product with phosphoryl chloride (cf. Marshall and Walker, *J.*, 1951, 1004) and purification by vacuum-sublimation; it had m. p. 34·8—35·2°. 4-Chloro-2-methylpyrimidine was prepared by Gabriel's method (*Ber.*, 1904, **37**, 3638) and crystallised to a constant m. p. of 56·5—57·0° from dry (Na) light petroleum (b. p. 40—60°). 2-Chloropyrimidine and 2-chloro-4-methylpyrimidine were prepared by Howard's method (U.S.P. 2,477,409) and recrystallised to a constant m. p. of 64·5° and 47·5°, respectively, from dry light petroleum (b. p. 60—80° and 40—60°, respectively). A pure sample of 2-chloro-4 : 6-dimethylpyrimidine, given by Dr. J. F. W. McOmie, to whom gratitude is expressed, was recrystallised from light petroleum (b. p. 40—60°) and had m. p. 38·0°. 2-Chloro-3-nitro- and 2-chloro-5-nitro-pyridine were prepared as described in Part I (*loc. cit.*).

2-Chloro-4-methyl-5-nitropyridine. This was obtained by converting 2-amino-4-methylpyridine (from the Reilly Tar and Chemical Co.) into a mixture, separable by steam-distillation, of 2-amino-4-methyl-3- and -5-nitropyridine by Seide's method (*Ber.*, 1924, **57**, 791). The latter amine was converted into the corresponding 2-chloro-compound by a method very similar to that described in Part I (p. 438) for 2-chloro-5-nitropyridine (cf. Lappin and Slezak, *J. Amer. Chem. Soc.*, 1950, **72**, 2806, for the hydroxy-compound). Decolorisation of a dark methanolic solution with charcoal, followed by crystallisation from methanol between room temp. and −30°, sublimation at 50°/0·7 mm., and further recrystallisation gave *2-chloro-4-methyl-5-nitropyridine* (30%, overall yield 6·5%), m. p. 36·5° (Found: C, 41·9; H, 3·1; N, 16·3; Cl, 20·6. $C_6H_5O_2N_2Cl$ requires C, 41·8; H, 2·9; N, 16·2; Cl, 20·6%).

Amines. Piperidine ("Special Grade" free from pyridine and tetrahydropyridine, from Robinson Bros. Ltd.) was dried twice over potassium hydroxide and twice over sodium and twice fractionated (50 × 1·5 cm. column packed with Fenske helices), and a fraction of b. p. 106·4°/760·0 mm. (corr.), $n_D^{20\cdot0}$ 1·4537, was collected (cf. Davies and McGee, *J.*, 1950, 678). Morpholine (from British Drug Houses Ltd.) was similarly purified and had b. p. 128·4°/760·0 mm. (corr.), $n_D^{20\cdot0}$ 1·4549 (cf. Dermer and Dermer, *J. Amer. Chem. Soc.*, 1937, **59**, 1148). Pyridine, aniline, and *p*-toluidine were purified as described in Part I (*loc. cit.*).

Solvent. The 99·8% ethanol was prepared as in Part I.

Reaction Products.—These were usually isolated from solutions used in kinetic experiments, and were colourless oils unless otherwise indicated. 2-Piperidinopyrimidine had b. p. 129°/14 mm., its *picrate* m. p. 121° (Found: C, 45·4; H, 4·1; N, 21·9. $C_{15}H_{16}O_7N_6$ requires C, 45·9; H, 4·1; N, 21·4%). 4-Methyl-2-piperidinopyrimidine gave a *picrate*, m. p. 135° (Found: C, 46·9; H, 4·5; N, 20·2. $C_{16}H_{18}O_7N_6$ requires C, 47·3; H, 4·5; N, 20·7%). 2-Methyl-4-piperidinopyrimidine gave a *picrate*, m. p. 169° (Found: C, 47·6; H, 4·4; N, 20·3%). [This picrate is wrongly reported in *Chem. Abs.*, 1952, **46**, 5053, for that of the 2 : 6-dimethyl compound (cf. Andrisano and Modena, *loc. cit.*).] 6-Methyl-4-piperidinopyrimidine gave a *picrate*, m. p. 172° (Found: C, 47·7; H, 4·5; N, 20·7%). 4 : 6-Dimethyl-2-piperidinopyrimidine had m. p. 62°; Brown and Kon (*J.*, 1948, 2147) gave 60—61°. 3-*Nitro*-2-*piperidinopyridine* had m. p. 52° (Found: C, 57·6; H, 6·3; N, 20·9. $C_{10}H_{13}O_2N_3$ requires C, 57·9; H, 6·3; N, 20·3%). 5-Nitro-2-piperidinopyridine had m. p. 84°; Mangini (*Ric. Sci.*, 1937, **8**, I, 427) gives 83·5—84·5°. 4-*Methyl*-5-*nitro*-2-*piperidinopyridine* had m. p. 91° (Found: C, 59·7; H, 6·8; N, 19·7. $C_{11}H_{15}O_2N_3$ requires C, 59·7; H, 6·8; N, 19·0%).

2-Morpholinopyrimidine gave a *picrate*, m. p. 153° (Found: C, 42·6; H, 3·4; N, 21·3. $C_{14}H_{14}O_8N_6$ requires C, 42·6; H, 3·6; N, 21·3%). 4-Methyl-2-morpholinopyrimidine, a low-melting solid, gave a *picrate*, m. p. 140° (Found: C, 44·2; H, 4·0; N, 20·4. $C_{15}H_{16}O_8N_6$ requires C, 44·1; H, 4·0; N, 20·6%). 2-*Methyl*-4-*morpholinopyrimidine* formed a *monohydrate*, m. p. 35° (Found: C, 55·3; H, 7·7; N, 21·2. $C_9H_{13}ON_3,H_2O$ requires C, 54·8; H, 7·7; N, 21·3%). 6-*Methyl*-4-*morpholinopyrimidine* had m. p. 93° (Found: C, 60·7; H, 7·3; N, 23·3. $C_9H_{13}ON_3$ requires C, 60·3; H, 7·3; N, 23·4%). 4 : 6-*Dimethyl*-2-*morpholinopyrimidine* had m. p. 56·5° (Found: C, 61·9; H, 7·8; N, 21·1. $C_{10}H_{15}ON_3$ requires C, 62·2; H, 7·8; N, 21·7%). 2-Morpholino-5-nitropyridine, had m. p. 142°; Cragoe and Hamilton (*J. Amer. Chem. Soc.*, 1945, **67**, 536) give m. p. 142·3—143·3°. 4-*Methyl*-2-*morpholino*-5-*nitropyridine* had m. p. 159° (Found: C, 54·0; H, 6·0; N, 18·5. $C_{10}H_{13}O_3N_3$ requires C, 53·8; H, 5·9; N, 18·8%).

Procedure.—This was as described in Parts I and II, but blank experiments showed that the chloro-compounds did not interfere with the Volhard determination of chloride ion, so it was unnecessary to extract unchanged chloro-compounds before analysing aliquot portions of the reaction solution.

Results

Detailed values for some of the reactions of secondary amines are given in Table 1, and all the results with these are summarised in Table 2. Evidence of overall order of reaction is

Table 1.

Reactions of piperidine.

2-*Chloropyrimidine at* 30·0°. (i) a = 0·4225M.

Time (min.)	5·0	10·0	17·0	25·0	35·0	50·0	70·0	90·0
Decompn., %	8·5	15·6	24·4	32·5	42·1	52·6	63·5	70·8
10^4k	—	6·79	6·82	6·68	6·90	6·87	6·93	6·84

Mean $k = 6{\cdot}83 \pm 0{\cdot}05 \times 10^{-4}$; 50% decompn. at 47·0 min.

(ii) a = 0·2113M, b = 0·0500M; mean $k = 6{\cdot}62 \pm 0{\cdot}08 \times 10^{-4}$; 50% decompn. at 95·0 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}02$. Effective ratio of concentrations = 2·00. Order with respect to piperidine 0·99; with respect to 2-chloropyrimidine 1·00 (by differential method).

2-*Chloro*-4 : 6-*dimethylpyrimidine at* 40·0°. (i) a = 0·3983M.

Time (min.)	10·0	20·0	40·0	75·0	120·0	195·0	270·0	375·0
Decompn., %	3·5	8·1	16·9	28·8	41·4	55·8	66·2	75·4
10^4k	—	(1·94)	2·19	2·13	2·16	2·13	2·14	2·09

Mean $k = 2{\cdot}14 \pm 0{\cdot}02 \times 10^{-4}$; 50% decompn. at 161 min.

(ii) a = 0·2019M, b = 0·0500M; mean $k = 2{\cdot}33 \pm 0{\cdot}03 \times 10^{-4}$; 50% decompn. at 306 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 1{\cdot}90$. Effective ratio of concns. = 1·96.

2-*Chloro*-4-*methyl*-5-*nitropyridine at* 30·0°. (i) a = 0·3768M, b = 0·1000M.

Time (min.)	5·0	10·0	17·0	23·0	33·0	45·0	60·0	80·0
Decompn., %	10·9	20·9	33·2	42·2	54·2	64·0	73·1	81·1
10^3k	—	(1·15)	1·21	1·25	1·30	1·30	1·32	1·32

Mean $k = 1{\cdot}28 \pm 0{\cdot}04 \times 10^{-3}$; 50% decompn. at 28·5 min.

(ii) a = 0·1980M, b = 0·0500M; mean $k = 1{\cdot}26 \pm 0{\cdot}01 \times 10^{-4}$; 50% decompn. at 55·0 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 1{\cdot}93$. Effective ratio of concns. = 1·83

TABLE 1. (*Continued*).

Reactions of morpholine.

2-*Chloropyrimidine at* 30·0°. (i) $a = 0{\cdot}4258$M.

Time (min.)	15·0	30·0	50·0	75·0	105·0	150·0	198·0	300·0
Decompn., % ...	5·2	10·3	16·6	22·9	31·0	40·2	48·5	61·3
10^4k	—	1·51	1·51	(1·44)	1·52	1·51	1·52	1·50

Mean $k = 1{\cdot}51 \pm 0{\cdot}02 \times 10^{-4}$; 50% decompn. at 207 min.

(ii) $a = 0{\cdot}2045$M, $b = 0{\cdot}0500$M; mean $k = 1{\cdot}54 \pm 0{\cdot}03 \times 10^{-4}$; 50% decompn. at 420 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}03$. Effective ratio of concns. = 2·09. Order with respect to morpholine 1·05; with respect to chloro-compound 0·97 (by differential method).

4-*Chloro*-2-*methylpyrimidine at* 20·0°. (i) $a = 0{\cdot}3976$M.

Time (min.) ...	10·0	20·0	30·0	45·0	60·0	83·0	110·0	140·0	170·0
Decompn., % ...	8·99	17·3	24·7	33·6	42·1	51·7	60·7	67·9	74·0
10^4k	—	4·31	4·34	4·25	4·39	4·37	4·40	4·35	4·39

Mean $k = 4{\cdot}35 \pm 0{\cdot}04 \times 10^{-4}$; 50% decompn. at 77·5 min.

(ii) $a = 0{\cdot}1988$M, $b = 0{\cdot}0500$M; mean $k = 4{\cdot}23 \pm 0{\cdot}04 \times 10^{-4}$; 50% decompn. at 156 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}01$. Ratio of concns. = 2·00.

FIG. 1.

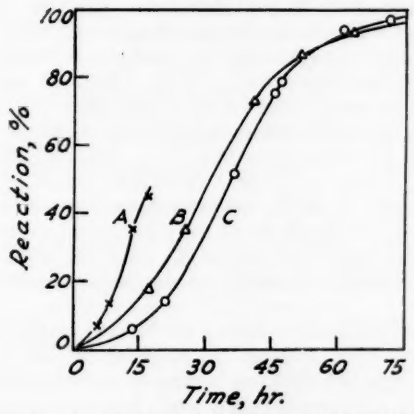


FIG. 2.

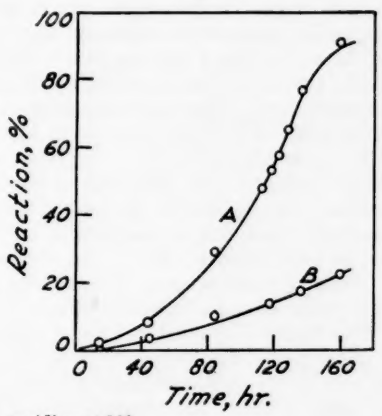


FIG. 1. *A. Reaction of* 4-*chloro*-6-*methylpyrimidine with pyridine at* 80°.
B and C. Reactions of 2-*chloropyrimidine with* p-*toluidine and aniline respectively at* 80°.

FIG. 2. *A and B. Reactions of* 2-*chloro*-4 : 6-*dimethylpyrimidine with pyridine at* 90° *and* 80° *respectively.*

TABLE 2.

	Piperidine			Morpholine		
Chloro-compound	20·0° (i)	30·0° (i)	40·0° (i)	20·0° (i)	30·0° (i)	40·0° (i)
2-Chloropyrimidine	32·2—34·3	67·9—69·3	125—132	7·48—7·94	15·0—15·2	27·6—29·3
2-Chloro-4-methylpyrimidine ...	13·4—14·0	28·0—29·2	52·7—55·5	3·26—3·32	6·59—6·86	13·7—14·2
2-Chloro-4 : 6-dimethylpyrimidine	5·55—5·80	11·0—11·5	20·9—21·9	1·35—1·38	2·69—2·88	5·31—5·59
4-Chloro-2-methylpyrimidine ...	162—167	292—308	512—532	42·5—44·0	75·8—78·7	132—138
4-Chloro-6-methylpyrimidine * ...	113—116	213—217	356—382	28·1—29·5	55·4—55·7	97·5—98·9
2-Chloro-3-nitropyridine †	217—221	413—426	764—792	—	—	—
2-Chloro-5-nitropyridine †	345—354	663—678	1180—1230	—	—	—
2-Chloro-4-methyl-5-nitropyridine †	63·9—65·9	121—132	237—247	—	—	—

(i) Extreme values of 10^5k in l. mole^{-1} sec.$^{-1}$ for a given experiment. Not less than 70% of the reaction was usually studied. (For mean k's at 30·0°, see Table 3.) Values of x at "infinite" time always corresponded to 99·8—100·0% reaction.

* For this compound, $k = 2{\cdot}82 \times 10^{-5}$ at 0° and $5{\cdot}28 \times 10^{-5}$ at 8·6°.

† $a = 0{\cdot}2$M, $b = 0{\cdot}0500$M.

given for selected examples, and of the order with respect to each reactant, determined by the differential method (Laidler, "Chemical Kinetics," New York, 1950, p. 14), for reactions of 2-chloropyrimidine. The experimentally observed times are recorded in min., but the velocity

coefficients are given in the usual units, viz., l. mole^{-1} sec.$^{-1}$. Errors in k given after the $\pm$ sign are mean deviations from the mean. Temperatures are accurate to $\pm 0{\cdot}03°$. As usual, the second-order velocity coefficient, k, is given by

$$k = \frac{1}{2t(0{\cdot}5a - b)} 2{\cdot}303 \log_{10} \frac{b}{0{\cdot}5a} \cdot \frac{0{\cdot}5a - x}{b - x}$$

where a is the initial amine concentration (nearly either 0·4 or 0·2M) and b is the initial chloro-compound concentration (either 0·1000 or 0·0500M). Because of the relative rapidity of the reactions, velocity coefficients were calculated by using the time of the first observation as the effective zero, so no values of k are given corresponding to the first time observation.

The courses of the reactions of aniline, *p*-toluidine, and pyridine with certain chloropyrimidines are displayed in Figs. 1 and 2.

Discussion

Mechanism of the Substitution Process.—Although the stereochemical difficulties discussed by Chapman and Parker (*J.*, 1951, 3301) do not apply to the formation of " intermediates of some stability " (cf. Bunnett and Zahler, *Chem. Reviews*, 1951, **49**, 299) in the reactions under consideration, yet it seems unnecessary to postulate this. Whereas in electrophilic aromatic substitution there is crucial evidence, in the case of aromatic nitration, favouring the formation of a complex between the nitronium ion and the aromatic system, there is no such evidence relating to the reactions which are the subject of this communication. The reaction solutions do not develop colour—this is also observed in the reactions of pyridine bases with halogenonitropyridines during most of the reaction—nor has a search of the literature revealed examples of complex formation, either of the " Meisenheimer " type (Bunnett et al., *loc. cit.*, p. 304) or of the " molecular " type (cf. Landauer and McConnell, *J. Amer. Chem. Soc.*, 1952, **74**, 1221), between pyrimidine derivatives and piperidine or morpholine. Although conceding some of the advantages of the " stable intermediate " theory (cf. Berliner, Quinn, and Edgerton, *ibid.*, 1950, **72**, 5305), we prefer, for the present, to treat the reactions under discussion as simple bimolecular nucleophilic aromatic substitutions.

The results displayed in Figs. 1 and 2 provide evidence in favour of the acid catalysis of nucleophilic displacements from basic heterocyclic systems investigated by Banks (*loc. cit.*), by Maggiolo and Phillips (*J. Org. Chem.*, 1951, **16**, 376) and by Morley and Simpson (*J.*, 1949, 1014). The strongly acidic anilinium or *p*-toluidinium ions, formed by the reactions which are the subject of Fig. 1, protonate the 2-chloropyrimidine in increasing proportion as the reaction proceeds, resulting in a typical autocatalytic process. It was surprising to find the same phenomenon with pyridine as reagent, for its reactions apparently generate no acid. However, the autocatalytic effect is very marked (Figs. 1 and 2). For the reaction of 2-chloropyrimidine with pyridine in ethanol at 90°, the " apparent " second-order rate coefficient increases linearly with percentage reaction (x) according to the law $10^6k = 0{\cdot}063x + 4{\cdot}3$. We tentatively ascribe this to solvolysis, with the liberation of protons, of the 2′-pyrimidylpyridinium chloride presumably produced first. Moreover, the absence of autocatalysis with amines of sufficiently great basic strength is readily understood, and in contrast with other chloro-heterocyclic compounds, the uncatalysed reactions of the chloropyrimidines occur at measurable speeds at ordinary temperatures (cf. Morley and Simpson, *loc. cit.*).

One of us has shown that in these reactions the ratio, α_n, of the rate of ethanolysis to that of the main reaction at $n\%$ " apparent reaction " is given by $\alpha_n = \{c[R_2H_2N^+]\}^{-1}$, where $c = k_4/k_2K_b$ (cf. Part II, p. 3394, and Bunnett and Zahler, *loc. cit.*, p. 344). Taking k_2 as $1{\cdot}0 \times 10^{-3}$ (Russell-Hill, unpublished) and k_4 as $3{\cdot}3 \times 10^{-4}$ for the reactions of 2-chloropyrimidine at 20°, and K_b as not greater than 10^{-6} (cf. Hägglund, *J. Chem. Phys.*, 1942, **10**, 215; Cavell and Chapman, *Chem. and Ind.*, 1953, 1266), we find $\alpha_n \not> 1/300n$, so that in this case ethanolysis may be neglected. The same conclusions almost certainly hold for the remaining reactions, especially those of morpholine, a much weaker base than piperidine. Moreover, this disposes of the possibility that the steady rate coefficients

observed may be due to a fortuitous combination of falling values caused by ethanolysis and rising values caused by acid-catalysis.

Influence of Nuclear Methyl Groups on the Reactivity of Chloropyrimidines and Related Nitro-compounds.—Nuclear *meta*-methyl groups influence these nucleophilic displacements in two ways: by inductive electron release to the seat of substitution, and, when *ortho* to an activating nitro-group, by steric inhibition of the conjugation of the nitro-group with the aromatic system, so that the configuration of the system depends on a compromise between steric compression energy and loss of stabilisation by conjugation. The purely polar effect of a *para*-methyl group has been measured by Berliner and Monack (*J. Amer. Chem. Soc.*, 1952, **74**, 1574): E is raised by 1100 cal. (cf. also Bevan, Hughes, and Ingold, *Nature*, 1953, **171**, 301). *meta*-Methyl groups inserted in chloro-2 : 4-dinitrobenzene have been studied by Miller and his associates (*J.*, 1952, 3550; 1953, 1475), who observed a diminution of rate by a factor of 5·4 at 0° and 2·6 at 100·8°. Our own results (Table 2) show that a *meta*-methyl group substituted into 2-chloropyrimidine reduces the reaction rate by a factor of ~2·4 and a second group has a very similar effect, for reactions of both piperidine and morpholine in the temperature range 20—40°. The same uniformity is not, however, observed in the Arrhenius parameters (Table 3). For reactions of piperidine, the

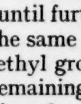
TABLE 3.

Chloro-compound	Amine	30·0°, 10^4k	E (cal./mole)	$\log_{10} A$
2-Chloropyrimidine	Piperidine	6·70	12,400	5·7
	Morpholine	1·52	12,300	5·0
2-Chloro-4-methylpyrimidine	Piperidine	2·80	12,500	5·4
	Morpholine	0·691	13,000	5·2
2-Chloro-4 : 6-dimethylpyrimidine	Piperidine	1·13	12,100	4·8
	Morpholine	0·281	12,600	4·5
4-Chloro-2-methylpyrimidine	Piperidine	30·0	10,600	5·1
	Morpholine	7·71	10,700	4·6
4-Chloro-6-methylpyrimidine	Piperidine	21·4	11,000	5·2
	Morpholine	5·55	11,100	4·7
2-Chloro-3-nitropyridine	Piperidine	41·9	12,000	6·2
2-Chloro-5-nitropyridine	Piperidine	67·1	11,500	6·1
2-Chloro-4-methyl-5-nitropyridine	Piperidine	12·6	12,400	6·0

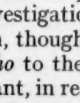
Units of A and k are l. mole^{-1} sec.$^{-1}$. Energies of activation are accurate to ±300 cal., values of $\log_{10} A$ to ±0·3 unit. The values of k are mean values from independent determinations and are accurate to ±2%.

variations in E are barely significant, but there is a steady downward trend in log A. Any explanation of these observations must at present be rather speculative, so we defer discussion of this point until further investigations are complete. The reactions of morpholine fall roughly within the same pattern, though there are some anomalies.

Insertion of a methyl group *ortho* to the nitro-group in 2-chloro-5-nitropyridine raises E by ~1000 cal., A remaining constant, in reactions with piperidine: a similar phenomenon is observed with chloro-2 : 4-dinitrobenzene where E is raised by 1400 cal. (B. Capon, unpublished work). It is clear that steric inhibition of the conjugation of the nitro-group has more effect than the purely polar effect in methylpyrimidine derivatives, though not than that measured by Berliner and Monack (*loc. cit.*).



(I)



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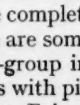


(III)

(IV)

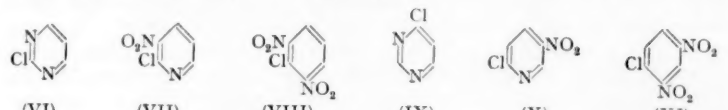
(V)

	(I)	(II)	(III)	(IV)	(V)
E (cal.)	12,500	10,600	11,000	12,400	19,900
log A	5·4	5·1	5·2	5·7	5·5

* D. Q. Russell-Hill, unpublished.

Reactivity of 2- and 4-Chloropyrimidine Derivatives.—The instability of 4-chloropyrimidine precludes direct comparison of the mobility of chlorine in the 2- and the 4-position of the pyrimidine nucleus. However, direct comparison can be made in methylated derivatives as shown above (reactions of piperidine). The isomeric change on going from (I) to (II) results in a fall in E of ~2000 cal., and a slight fall in log A, a phenomenon very similar

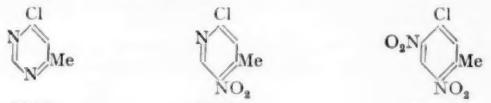
to that reported in Part II (p. 3394) for reactions of chloronitropyridines with pyridine bases. This is attributable to the difference between an *ortho*- and a *para*-quinonoid transition state. Unfortunately, quantum-mechanical analysis of this type of problem (cf. Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 283) does not seem to be sufficiently discriminating to yield useful results. An estimate of the Arrhenius parameters for the reactions of 4-chloropyrimidine itself may be obtained by comparing the observed values for compounds (I)—(IV), giving a log A value of ~5·0 and an upper limit to E of ~10,500 cal. Comparison of the results for (IV) and (V) indicates that variation of structure within the pyrimidine field is of small importance relative to the insertion of the second hetero-atom, which reduces E by ~7500 cal. The comparable magnitude involved on passing from the benzene to the pyridine series is at least 7000 cal. (Part I, p. 446).



	(VI)	(VII)	(VIII)	(IX)	(X)	(XI)
E (cal.)	12,400	12,000	12,200 *	~10,500	11,500 †	10,200 ‡
log A	5·7	6·2	5·9	~5·0	6·1	5·6

* P. W. Soanes, unpublished. † Part I. ‡ Brady and Cropper, *J.*, 1950, 507.

Above are shown the effects of various cyclic nitrogen–exocyclic nitro-group transformations. In our view the similarity of the parameters for (VI) and (VIII) is largely fortuitous. The reaction parameters of (VI) are determined by absence of steric hindrance, *ortho*-quinonoid transition state, and weak inductive effect of cyclic nitrogen; those of (VIII) by a degree of steric inhibition of nitro-group–ring conjugation, powerful inductive effects of nitro-groups, and a " net *ortho*-effect " in which classical steric hindrance predominates. Compound (VII) occupies a roughly intermediate position. The results for (IX)—(XI) largely confirm those obtained in Part II.



	(XII)	(XIII)	(XIV)
E (cal.)	11,000	12,400	11,600 *
log A	5·2	6·0	6·3

* B. Capon, unpublished.

Considering the figures for (XII)—(XIV) and for (X) and (XI), we estimate that the " correction " for the steric effect of a methyl group *ortho* to a nitro-group *para* to the seat of substitution is an increase in E of 900—1400 cal., so that the net effect of replacing cyclic nitrogen by $\geqslant C\text{–}NO_2$ in (XII) is largely in the log A term. This analysis is, however, only tentative since the reactions of compounds (X)—(XIV) do not constitute an isoentropic series.

Throughout the foregoing, it has been assumed that formation of the transition state involves a change from trigonal towards tetrahedral hybridisation at the attacked carbon, with imposition of negative charge on ring nitrogen (cf. Ingold, " Structure and Mechanism in Organic Chemistry," London, 1953, p. 808, for a formulation of the transition state).

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THE UNIVERSITY, SOUTHAMPTON. [*Received, November 2nd*, 1953.]

Complex Fluorides of Quadri- and Quinque-valent Ruthenium.

By M. A. Hepworth, R. D. Peacock, and P. L. Robinson.

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Work on the complex fluorides of ruthenium has been continued; those involving the metal in the quadri- and quinque-valent states are described. Ability to prepare fluororuthenates of the type $M(I)RuF_6$ and $N(II)(RuF_6)_2$ depends upon the ionic radius of M(I) and N(II) and appears to be restricted to ions with values of 0·99 Å and above.

Before the subject was studied in these laboratories, the known halide complexes of quadrivalent ruthenium were restricted to those involving only chlorine or bromine. They had a co-ordination number of 6 and were of the types M_2RuCl_6 and $M_2RuCl_5(OH)$. Furthermore, the only quinquevalent compound of ruthenium described in the literature was the simple pentafluoride. The series of new compounds formulated below and now described show that this view of the fluorine chemistry of ruthenium calls for extensive revision.

Quadrivalent ruthenium : K_2RuF_6, Cs_2RuF_6.

Quinquevalent ruthenium : $KRuF_6$, $CsRuF_6$, $AgRuF_6$, $TlRuF_6$, $Ca(RuF_6)_2$, $Sr(RuF_6)_2$, $Ba(RuF_6)_2$.

Since the complexes of quadrivalent are derived from those of quinquevalent ruthenium, it is convenient to begin with the latter.

Complex Fluorides of Quinquevalent Ruthenium.—Recently it was shown (Aynsley, Peacock, and Robinson, *Chem. and Ind.*, 1952, 1002) that a white substance having a composition corresponding to K_2RuF_8 could be obtained by the action of elementary fluorine on potassium chlororuthenate at 200°. At the time, this was assumed to be a true complex fluoride of sexavalent ruthenium, principally on the evidence of *X*-ray photographs in which the accompanying presence of potassium fluoride or other potassium salt was not disclosed. Klemm (personal communication) has pointed out, however, that the magnetic behaviour of this material suggests that it is more probably a mixture of a new quinquevalent complex fluoride, potassium hexafluororuthenate(v), $KRuF_6$, and Bode and Wendt's potassium difluoride, KF_2 (*Naturwiss.*, 1950, **37**, 477). The preparation of the pure potassium hexafluororuthenate(v), described below, and its *X*-ray examination leave little doubt as to the correctness of this view.

In the course of a further investigation of these complexes we have used bromine trifluoride as the fluorinating agent (cf. Sharpe, *J.*, 1950, 3444). Metallic ruthenium reacts violently at room temperature with this reagent, forming a brownish solution which, after removal of the solvent in a vacuum at room temperature, yields a pale cream solid bromofluoride with the composition $RuBrF_8$. When heated to 120° in a vacuum, this compound melts with decomposition forming emerald-green droplets of ruthenium pentafluoride, RuF_5, and bromine trifluoride which volatilises easily: $RuBrF_8 \longrightarrow RuF_5 + BrF_3$. Prepared in this manner, ruthenium pentafluoride can be readily purified by a simple vacuum-distillation into a side-arm receiver where it condenses and sets to a pale green crystalline mass. Under the rigorously dry conditions of this preparation, ruthenium pentafluoride can be conveniently handled in glass apparatus with very little evidence of attack. Indeed, this operation probably constitutes the easiest method of obtaining in a pure form the highly reactive and deliquescent pentafluoride.

Of special interest is the reaction of bromine trifluoride with a mixture of potassium bromide and ruthenium metal in the ratio KBr : Ru = 1 : 1. This leads to the formation of a new complex fluoride, potassium hexafluororuthenate(v), $KRuF_6$, which had an *X*-ray pattern identical with that of the material previously reported as K_2RuF_8. That the former is the true complex fluoride of ruthenium was demonstrated in the course of an examination of the products resulting from the action of bromine trifluoride on mixtures of potassium bromide and ruthenium metal in the ratios KBr : Ru = 1 : 2, 2 : 1, and 3 : 1. The residue from the ruthenium-rich mixture, on being heated to 120° in a vacuum, evolved

ruthenium pentafluoride and left $KRuF_6$ behind; the products from the other two mixtures, after being heated at 180° in a vacuum, contained, respectively, 1 and 2 equivs. of potassium fluorobromite, $KBrF_4$. Assuming the compound $RuBrF_8$ to be formulated as $(BrF_2)^+(RuF_6)^-$, we may postulate the following reaction as leading to the formation of $KRuF_6$:

$$KBrF_4 + (BrF_2)^+(RuF_6)^- \longrightarrow KRuF_6 + 2BrF_3$$

Similar reactions involving cæsium chloride and silver bromide lead to the formation of the cæsium and silver salts, $CsRuF_6$ and $AgRuF_6$, respectively. The corresponding salts of the bivalent alkaline earth barium, strontium, and calcium metals, which have the general formula $N(RuF_6)_2$ may also be prepared by using the bromate of the particular metal along with its equivalent of ruthenium.

On the other hand, attempts to obtain the sodium salt by treating 1 : 1 or 2 : 1 equivalent mixtures of sodium bromide and ruthenium failed. Presumably the salt $NaRuF_6$ is completely solvolysed in bromine trifluoride to $NaBrF_4$ and $RuBrF_8$. The residues when heated above 120° in a vacuum lost the whole of their ruthenium as the volatile pentafluoride, RuF_5. A similar result attends the heating of the product from the action of bromine trifluoride on a 1 : 1 equivalent mixture of thallous bromide and ruthenium; in this instance, however, the issue is complicated by the fact that 80—90% of the thallium is oxidised to the thallic form when dissolved in bromine trifluoride (Emeléus and Sharpe, *J.*, 1948, 2135). These results accord well with the behaviour of iron. We find that the action of elementary fluorine at 300° on an intimate mixture of iron and ruthenium, both in the metallic form, leads to the separate formation of ruthenium pentafluoride, which distils as it is produced, and of ferric fluoride, which remains behind. It is not obvious why certain metallic ions, *e.g.*, Na^+, fail to form salts with the RuF_6^- ion; but it seems fairly certain that the radius of the cation is involved. This is clearly demonstrated by the behaviour of the metal thallium which, as pointed out above, fails entirely to form a thallic salt, and yet can, given suitable conditions, yield the thallous salt, $Tl(I)RuF_6$. These conditions we have realised by using the hitherto unexploited fact that thallous fluoride is soluble in selenium tetrafluoride to form thallous selenofluorite, $Tl(I)SeF_5$ (Aynsley, Peacock, and Robinson, *J.*, 1952, 1231). By mixing solutions of ruthenium pentafluoride and thallous fluoride, each in selenium tetrafluoride, the thallous hexafluororuthenate(v), $TlRuF_6$, is formed. When this series of complex fluorides is tabulated against the values for the ionic radius of the respective cations (data from Wells, " Structural Inorganic Chemistry," Oxford Univ. Press, 1945, p. 93), the influence of this factor on the ability of the cation to form a ruthenium(v) salt is clearly displayed. Cations with a radius below about 0·99 Å appear to be ineffective.

Cation	Ionic radius (Å)	Salt	Cation	Ionic radius (Å)	Salt	Cation	Ionic radius (Å)	Salt
K^+	1·33	$KRuF_6$	Ba^{++}	1·35	$Ba(RuF_6)_2$	Na^+	0·95	None
Cs^+	1·69	$CsRuF_6$	Sr^{++}	1·12	$Sr(RuF_6)_2$	Tl^{+++}	0·95	None
Ag^+	1·26	$AgRuF_6$	Ca^{++}	0·99	$Ca(RuF_6)_2$	Fe^{+++}	0·60	None
Tl^+	1·44	$TlRuF_6$						

The complex salts just mentioned are cream-coloured solids, with the exception of those of silver and thallium(I), which are orange. They are all stable in dry air. The barium salt did not commence to decompose in a vacuum below 400°: it evolved a fume of ruthenium pentafluoride. In moist air the salts are rapidly attacked; they blacken on the surface and have the odour of ruthenium tetroxide, RuO_4. Their behaviour with water, which decomposes them rapidly, is complicated: it has been studied in detail and is described below.

Complex Fluorides of Quadrivalent Ruthenium.—When warmed with a small quantity of water, potassium and cæsium hexafluororuthenate(v) both slowly dissolve to give pale yellow solutions. The solutions evolve oxygen and have a decided smell of ruthenium tetroxide. When cooled they deposit crystals of potassium hexafluororuthenate(IV), K_2RuF_6, and the corresponding cæsium salt, respectively, as pale yellow plates. Further crops of less pure crystals may be obtained by adding concentrated solutions of potassium

or cæsium fluoride to the respective mother-liquors. The evidence leads us to believe that reaction may be represented by equation (1), but the fact that ruthenium tetroxide is

$$4RuF_6^- + 2H_2O \longrightarrow 4RuF_6^{--} + 4H^+ + O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

produced at the same time as the oxygen must indicate a certain degree of concurrent disproportionation, most probably according to (2). The amount of Ru(VIII) (*i.e.*, Ru as RuO_4) produced is, however, very small, and the disproportionation shown in (2) probably involves less than 10% of the material which originally reacted with water.

$$4Ru(V) \longrightarrow Ru(VIII) + 3Ru(IV) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Potassium hexafluororuthenate(IV) is slightly soluble in water, giving a colourless solution in which the compound is not immediately hydrolysed, but which decomposes in 1—2 hr. with precipitation of black, hydrated ruthenium dioxide. Exactly as has been found by Sharpe (*J.*, 1950, 3444) for the corresponding platinum salt, K_2PtF_6, there is no interaction with chloride ions in the absence of hydrogen ions. In the presence of these, however, as when hydrochloric acid is used, the reaction

$$RuF_6^{--} + 6Cl^- \xrightarrow{H^+} RuCl_6^{--} + 6F^-$$

proceeds; its course is shown by the development of an intense red-brown colour in the solution, readily recognisable as due to the chlororuthenate ion. The rate is accelerated by warming of the solution and by increase in the concentration of the acid.

Experimental

Reagents.—Bromine trifluoride was prepared from bromine which had been dried (P_2O_5) and distilled in a vacuum. Over this was passed, at the rate of 6 g./hr., hydrogen fluoride-free fluorine diluted with nitrogen, the reaction taking place in a Pyrex vessel cooled in a bath of cold water. The product was distilled in a vacuum, and the middle fraction employed by condensing it on the reactants. Ruthenium metal, in the form of a fine powder, was dried in a vacuum along with the other solids before use. Because chlorides were found to give products of a somewhat different colour and generally of a less reactive character, bromides were selected in the case of the alkali metals; and because of the deliquescence of the simple halide, bromates in that of the alkaline-earth metals.

Fluorides of Quinquevalent Ruthenium.—Ruthenium with bromine trifluoride. The reaction began at 10—15° with liberation of bromine and of sufficient heat to raise the metal rapidly to incandescence; but the action was readily controlled by appropriate cooling with liquid oxygen. Care was required, however, when the quantities used reached the order of 1 g. The removal of excess of bromine trifluoride in a vacuum at room temperature left a cream-coloured solid, $RuBrF_8$, (Found: Ru, 30·8%; equiv., 326. $RuBrF_8$ requires R, 30·5%; equiv., 333·7); this new *ruthenium bromo-octafluoride* reacts vigorously with water, giving a black precipitate of hydrated ruthenium dioxide, some ruthenium tetroxide, and hydrolysis products of bromine trifluoride. When heated to 120° in a vacuum, it melts with decomposition, forming ruthenium pentafluoride and bromine fluorides. By raising the temperature to 150—160° and maintaining the vacuum, the ruthenium pentafluoride can be readily distilled into a side-arm receiver where it condenses to a pale green crystalline mass (Found: Ru : F = 1 : 4·95).

Mixtures of ruthenium and potassium bromide with bromine trifluoride. (*a*) Mixture, Ru : KBr = 1 : 1. Reaction occurred at room temperature with formation of a cream precipitate insoluble in excess of bromine trifluoride. When this excess had been removed in a vacuum, the product was heated to 180° for 30 min. and yielded *potassium hexafluororuthenate*(V), a cream-coloured powder (Found: Ru, 39·4; K, 15·3; F, 44·5. $KRuF_6$ requires Ru, 39·9; K, 15·2; F, 44·9%). The quinquevalency was established by liberation of iodine from potassium iodide using Crowell and Yost's method (*J. Amer. Chem. Soc.*, 1928, **50**, 37).

(*b*) Mixture, Ru : KBr = 2 : 1. The product, after the excess of bromine trifluoride had been removed in a vacuum, evolved, on further heating to 120° in a vacuum, half the ruthenium present as ruthenium pentafluoride. Clearly it was a mixture of potassium hexafluororuthenate(V) and ruthenium bromo-octafluoride, $RuBrF_8$.

(*c*) Mixtures, Ru : KBr = 1 : 2 and 1 : 3. Again the products were mixtures. After being heated at 180° in a vacuum for 1 hr. the residue consisted of *complexes* of $KRuF_6$ with respectively 1 and 2 equivs. of potassium tetrafluorobromite, $KBrF_4$ (Found: equiv., 440.

$KRuF_6,KBrF_4$ requires equiv., 449. Found: equiv., 625. $KRuF_6,2KBrF_4$ requires equiv., 644).

Preparation of cæsium, silver, barium, calcium, and strontium salts. The fluorination by bromine trifluoride of a 1 : 1 mixture of cæsium chloride and ruthenium metal yielded *cæsium hexafluororuthenate*(V) as a creamy-white solid, sparingly soluble in bromine trifluoride (Found: Ru, 28·4; Cs, 38·0. $CsRuF_6$ requires Ru, 29·2; Cs, 38·2%). In a similar manner, the *silver* salt is formed, as an orange powder soluble in bromine trifluoride, on use of a 1 : 1 mixture of silver bromide and ruthenium metal (Found: Ru, 32·0; Ag, 32·7. $AgRuF_6$ requires Ru, 31·3; Ag, 33·4%). For the corresponding salts of the alkaline earths, mixtures of their bromates and ruthenium metal in the molecular proportions 1 : 2 were treated with bromine trifluoride. The products, which were slightly soluble in bromine trifluoride, could be heated to 200° in a vacuum without evolving any ruthenium pentafluoride, and left as residues a cream-coloured powder in every case [Found: Ru, 42·7; F, 47·6. $Ca(RuF_6)_2$ requires Ru, 43·1; F, 48·4. Found: Ru, 38·6; F, 44·4. $Sr(RuF_6)_2$ requires Ru, 39·1; F, 44·0. Found: Ru, 34·1; F, 39·5%; Ba equiv., 561. $Ba(RuF_6)_2$ requires Ru, 35·6; F, 40·0%; Ba equiv., 568]. In order to ascertain approximately the stability of these *compounds*, the barium salt was heated in a vacuum, through a rising range of temperature; decomposition was first observed at 400° owing to evolution of a green fume (probably ruthenium pentafluoride). At higher temperatures ruthenium pentafluoride was released in some quantity with the expected marked attack on, and blackening of, the apparatus.

Preparation of thallous salt, $TlRuF_6$. Ruthenium pentafluoride was prepared as described above by the action of bromine trifluoride on ruthenium metal followed by heating of the product to 140° in a vacuum, the excess of bromine trifluoride having been removed from the apparatus by sealing off the trap in which it had been condensed. Selenium tetrafluoride, prepared according to Aynsley, Peacock, and Robinson (*loc. cit.*), was distilled on to the ruthenium pentafluoride in an evacuated apparatus, and simultaneously on to the calculated quantity of thallous fluoride in a bulb attached to the main apparatus by a " Quickfit " joint, lubricated with C.F.L.4 Fluorolube. Both bulbs were warmed to dissolve the respective solids in the selenium tetrafluoride. The ruthenium pentafluoride dissolved readily to give a clear, yellowish-green liquid. The solution of thallous pentafluoroselenate, $TlSeF_5$, was frozen and the ruthenium pentafluoride solution poured over the solid; on warming, a yellow to buff-coloured precipitate formed at the liquid–solid interface and spread throughout as liquefaction took place and the solutions mixed. The excess of selenium tetrafluoride was removed under a vacuum, and the residue, after being heated to 160°, proved to be *thallous hexafluororuthenate*(V), a pale orange powder (Found: Tl, 48·0; Ru, 23·4; F, 28·0; Se, trace. $TlRuF_6$ requires Tl, 48·7; Ru, 24·2; F, 27·1%).

Potassium Hexafluororuthenate(IV).—$KRuF_6$ was treated with the minimum amount of water (15 ml. per g. of $KRuF_6$) and gently warmed until effervescence ceased and it had completely dissolved. The solution was kept below 80°, since boiling caused an irreversible hydrolysis to set in with the deposition of black, hydrated ruthenium dioxide. Immediately dissolution was complete the liquid was cooled to 0°; pale yellow plates of *potassium hexafluororuthenate*(IV) crystallised. These were collected on a sintered-glass filter, washed well with ice-cold water, then with carbon tetrachloride to remove any adhering traces of ruthenium tetroxide, and finally dried in a vacuum-desiccator (P_2O_5). A further crop of less pure crystals was obtained by adding a concentrated solution of potassium fluoride to the filtered mother-liquor, and was separated in exactly the same way (Found: Ru, 34·6; K, 26·3; F, 38·3. K_2RuF_6 requires Ru, 34·5; K, 26·6; F, 38·9%). The valency of the ruthenium was fixed by heating the compound to 90° for 1 hr. with a known excess of ceric ammonium sulphate solution, removing the ruthenium tetroxide thus formed by bubbling nitrogen through the solution, and determining the excess of ceric salt by titration with standard ferrous ammonium sulphate solution. 4 Equivs. of ceric salt were required per equiv. of ruthenium present in order to oxidise the latter to the octavalent state: *i.e.*, the valency of the ruthenium is $8 - 4 = 4$.

Potassium hexafluororuthenate(IV) is sparingly soluble in water to a colourless solution; immediately on warming this solution, or on keeping it at room temperature for upwards of an hour, black, hydrated ruthenium dioxide was precipitated. With hydrochloric acid the distinctive red-brown colour of the chlororuthenate ion, $RuCl_6^{2-}$, develop, the exchange being markedly catalysed by hydrogen ions. Thus both an increase in concentration of the acid and an increase in temperature were found to promote this change. In a similar manner, dilute sulphuric acid leads to the particular brown colour typical of a Ru(IV) sulphate solution.

Cæsium Hexafluororuthenate(IV).—By starting with $CsRuF_6$ and proceeding as just described,

this *cæsium* salt is obtained as pale yellow plates (Found: Ru, 20·4; Cs, 55·1; F, 24·1. Cs_2RuF_6 requires Ru, 21·0; Cs, 55·3; F, 23·7%). In physical and chemical properties it closely resembles the corresponding potassium salt.

Analyses.—Ruthenium. (*a*) In the absence of interfering elements, ruthenium was determined by hydrolytic precipitation, by sodium hydrogen carbonate from hydrochloric acid solution, of the hydrated dioxide, followed by ignition of the oxide and its reduction to the metal in hydrogen. (*b*) In other cases, *e.g.*, when alkaline-earth salts were present, the compound was dissolved in cold 10% hydrogen peroxide–sulphuric acid mixture; the fluorine was then removed by distillation as fluorosilicic acid, and the ruthenium remaining in the sulphate solution was distilled out as the tetroxide, after addition of potassium bromate. The distillate was received in ice-cold, 3% hydrogen peroxide, and the ruthenium recovered by addition of thionalide. The precipitated complex was ignited in air and reduced in hydrogen to the metal (Rogers, Beamish, and Russell, *Ind. Eng. Chem. Anal.*, 1940, **12**, 561).

Fluorine. This was determined as lead chlorofluoride either directly in the filtrate after removal of ruthenium, or, after the addition of concentrated sulphuric acid, in the distillate containing it as fluorosilicic acid.

Alkali metals. These were weighed as sulphates after reduction of the complex fluoride in hydrogen, extraction of the alkali fluoride from the residue in hot water, evaporation with sulphuric acid in a platinum dish, and ignition to dull red heat. Silver was determined as chloride.

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KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, November 25th*, 1953.]

The Mechanism of the Favorski Reaction.

By J. G. BURR, JUN., and M. J. S. DEWAR.

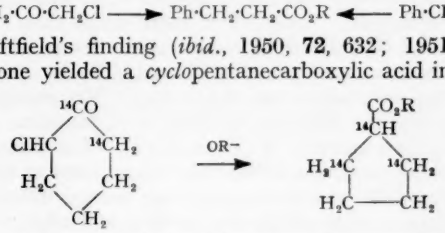
[Reprint Order No. 4876.]

Molecular-orbital analysis of the various intermediates which have been proposed for the Favorski reaction indicates that the reaction proceeds by loss of halogen from the initial carbanion to give the zwitterion suggested by Aston and Newkirk. This structure collapses into the *cyclo*propanone intermediate proposed by Loftfield, and final products result from the further reactions of this intermediate. The LCAO–MO calculations indicate that the conversion of the initial carbanion into the zwitterion is accompanied by an increase in conjugation energy, and this increase undoubtedly provides the driving force for the reaction.

IT has become apparent that in the Favorski reaction the two carbon atoms adjacent to the carbonyl group will, whenever possible, become equivalent. This was suggested by the discovery that two isomeric chloro-ketones gave the same rearranged product (McPhee and Klingsberg, *J. Amer. Chem. Soc.*, 1944, **66**, 1132) and has been unequivocally

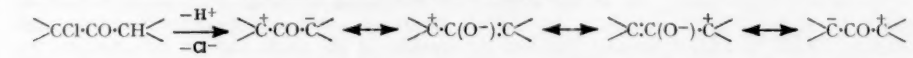
$$Ph{\cdot}CH_2{\cdot}CO{\cdot}CH_2Cl \longrightarrow Ph{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2R \longleftarrow Ph{\cdot}CHCl{\cdot}CO{\cdot}CH_3$$

demonstrated by Loftfield's finding (*ibid.*, 1950, **72**, 632; 1951, **73**, 4707) that [1 : 2-$^{14}C_2$]chloro*cyclo*hexanone yielded a *cyclo*pentanecarboxylic acid in which the isotope had



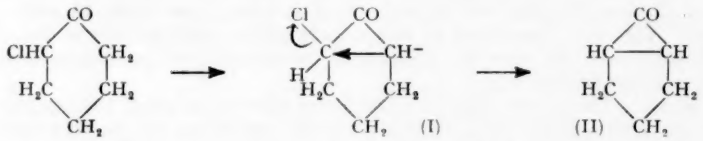
become equally distributed among the positions corresponding to the two α-carbon atoms of the chloro-ketone.

Two mechanisms have been advanced to explain this equivalence. Aston and Newkirk (*ibid.*, 1951, **73**, 3900) proposed the formation of a zwitterion whose various contributing resonance structures will account for the products observed :



This seems at first sight inadequate as there is no obvious driving force to explain the removal of a chlorine ion from a molecule already containing one formal charge.

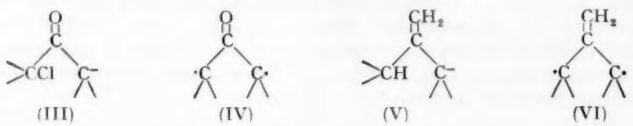
Loftfield suggested the formation of a *cyclo*propanone intermediate whose subsequent reactions also account for the equivalence of the two α-carbon atoms in the halogenoketone :



This mechanism also seems inadequate since in the preliminary ion (I) the negatively charged carbon atom is probably in a trigonal configuration coplanar with the carbonyl group, and the available π-electrons lie in *p*-orbitals perpendicular to that plane. The *p*-orbital of the negatively charged carbon atom thus cannot overlap significantly with orbitals of the carbon atom attached to chlorine, and so it is very difficult to see how any interaction between these carbon atoms could stabilize the S_N2 transition state for expulsion of the halogen with simultaneous formation of a three-membered ring.

Contrary to Loftfield's comment (*loc. cit.*) the zwitterions proposed by Aston and Newkirk are not resonance structures contributing to the stability of the *cyclo*propanone intermediate, since the two charged carbon atoms do not normally occupy the positions in space which they would have in the *cyclo*propanone structure and also since orbital symmetry thus required of the doubly charged structure would normally favour a system planar over five carbon atoms and the oxygen atom. This is impossible in (II).

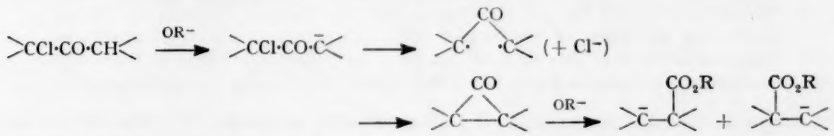
The first step in the reaction is undoubtedly the formation of a mesomeric carbanion (III). Aston and Newkirk's suggestion implies, in effect, that the intermediate (written as IV) has a much larger conjugation energy than (III), and that the conversion of (III) into (IV) is facilitated by the increase in conjugation energy.



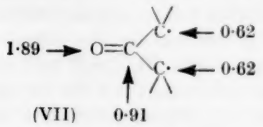
This possibility can be examined in two ways : First, one may compute the conjugation energies of (V) and (VI) which are isoconjugate with the ion (III) and the intermediate, (IV). The conjugation energies of these can be computed unambiguously by the standard LCAO–MO method and are 0·828β and 1·464β respectively, where β is the C–C resonance integral (with overlap neglected). Thus (VI) is more stable than (V) by 0·636β, and the difference between (III) and (IV) should be comparable. As an additional check, we have computed the total π-electron energies of (III) and (IV) by the same method, using reasonable values for the parameters (see Appendix). The energies found were 6·687β and 7·420β respectively, and the difference (0·733β) is of the same order of magnitude as that between the conjugation energies of (V) and (VI). The energy difference is indeed relatively insensitive to the parameters involved; thus, even in the limiting case where oxygen is considered infinitely electronegative, the energy difference changes only to 0·828β, (III) and (IV) degenerating effectively to vinyl and allyl.

The increase in conjugation energy on removal of chloride ion from (III) to give (IV) should therefore be very considerable (14 kcal. since β ~20 kcal.) and to this extent

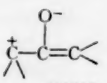
Aston and Newkirk's mechanism seems quite satisfactory. It is not immediately apparent how the intermediate (IV) could be converted into the observed final products. However, the calculated conjugation energy of (IV), although large (1·96β ~40 kcal.) is much less than the energy of formation of a C–C single bond (81 kcal.); therefore, even when allowance is made for the strain energy in a three-membered ring (30 kcal.), the conversion of (IV) into the isomeric *cyclo*propanone (II) should be exothermic. It seems reasonable to suppose that the intermediate (IV) is formed first and subsequently cyclizes to the Loftfield intermediate (II). Reaction of (II) with base then gives the observed final products. Our interpretation of the reaction is annexed.



In these calculations interactions between the non-bonded carbon atoms have been neglected. It is easily shown that such interactions should be bonding and should further stabilize the intermediate (IV) to some extent; the effect could not be large enough to make (IV) more stable than the isomeric *cyclo*propanone, although it should further facilitate the formation of (IV) from (III).



(VII)



(VIII)

The distribution of π-electrons in (IV) is of interest and is indicated in (VII). The structure approximates to one in which the oxygen atom carries a full formal negative charge, and each of the α-carbon atoms carries half a positive charge; in resonance terminology this would imply a major contribution from structures of the type (VIII).

Appendix

The calculations were carried out by the usual LCAO–MO method with neglect of overlap, and with the following parameters (cf. Bremmer and Bremmer, *J.*, 1950, 2335; Dewar, *Nature*, 1950, **166**, 790); $\alpha_0 = 2\beta$, $\beta_{C\text{-}O} = \beta_{C\text{-}C}\sqrt{2}$. No allowance was made for change in the coulomb integrals of carbon atoms adjacent to oxygen since such changes would not significantly affect calculations of relative energies.

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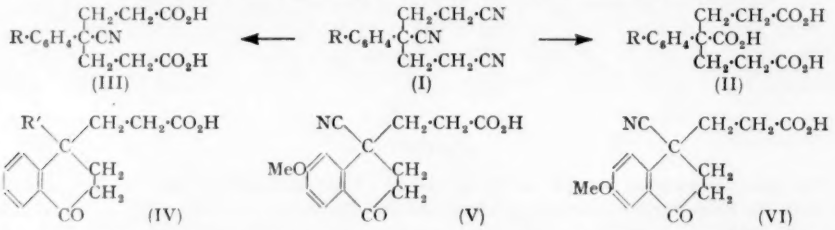
Intramolecular Acylation. Part IV. Preparation and Ring Closure of Some γ-Aryl-γ-carboxy- and -γ-cyano-pimelic Acids.*

By D. H. Hey and K. A. Nagdy.

[Reprint Order No. 4898.]

Methods are described for the preparation of γ-cyano-γ-phenylpimelic acid and its *m*- and *p*-methoxy-derivatives. Cyclodehydration of γ-carboxy-γ-phenylpimelic acid and of the above cyanophenylpimelic acids affords derivatives of β-(1 : 2 : 3 : 4-tetrahydro-4-oxo-1-naphthyl)propionic acid. The cyclisation of the γ-carboxy-acid provides further evidence of the deactivating influence of the nearer carboxyl group in an aryl-substituted polycarboxylic acid, but no such deactivating influence is found in the cyclisation of the γ-cyano-acids in which the nearer CO_2H group is replaced by CN.

γ-Cyano-γ-phenylpimelodinitrile (I; R = H) was prepared by Bruson and Riener (*J. Amer. Chem. Soc.*, 1943, **65**, 23) from benzyl cyanide and acrylonitrile, and Rubin and Wishinsky (*ibid.*, 1946, **68**, 828) showed that it could be hydrolysed with a mixture of sulphuric and acetic acids to γ-carboxy-γ-phenylpimelic acid (II; R = H). The latter workers also reported that hydrolysis with alkali gave γ-carbamyl-γ-phenylpimelic acid, but no details were given of the reaction conditions or the concentration of the alkali used. It is now shown that hydrolysis with boiling aqueous–alcoholic potassium hydroxide for seven hours gives γ-cyano-γ-phenylpimelic acid (III; R = H), and with the use of substituted benzyl cyanides this constitutes a general method for the preparation of γ-aryl-γ-cyanopimelic acids. Horning and Schock (*ibid.*, 1948, **70**, 2945) had previously reported that γ-cyano-γ-(2 : 3-dimethoxyphenyl)pimelic acid could not be obtained by the direct hydrolysis of γ-cyano-γ-(2 : 3-dimethoxyphenyl)pimelodinitrile but was obtained by conversion of the latter into the dimethyl ester followed by alkaline hydrolysis.



The new method has now been applied to the preparation of γ-cyano-γ-*m*- and -*p*-methoxyphenylpimelic acids (III; R = *m*-MeO and *p*-MeO) in addition to γ-cyano-γ-phenylpimelic acid itself. In the cyanoethylation reaction the *m*- and *p*-methoxybenzyl cyanides reacted less readily than the unsubstituted benzyl cyanides, requiring a longer time and more methanolic potassium hydroxide.

The γ-aryl-γ-carboxy- and -γ-cyano-pimelic acids thus made available provide suitable compounds from which further information may be obtained on the influence of the nearer CO_2H or CN group on intramolecular acetylation (cf. Part III, *loc. cit.*). It is known that γ-phenylpimelic acid, which lacks the nearer carboxyl group, can be converted readily into β-(1 : 2 : 3 : 4-tetrahydro-4-oxo-1-naphthyl)propionic acid and a neutral tricyclic diketone (von Braun and Weissbach, *Ber.*, 1931, **64**, 1785; Manske, *J. Amer. Chem. Soc.*, 1931, **53**, 1104). Similar attempts to effect ring closure of γ-carboxy-γ-phenylpimelic acid (II; R = H) by the action of aluminium chloride on the acid chloride in carbon disulphide failed to give consistent results. When benzene was used as a solvent a neutral compound, m. p. 137—139°, was obtained in good yield, which formed a 2 : 4-dinitrophenylhydrazone and a semicarbazone, but its structure has not been determined (cf. Horning and Schock, *J. Amer. Chem. Soc.*, 1948, **70**, 2941, and Johnson and Glenn, *ibid.*, 1949, **71**, 1092). On the other hand, the free γ-carboxy-γ-phenylpimelic acid readily underwent cyclodehydration

* Part III, *J.*, 1953, 1894.

with sulphuric acid in 43% yield and with polyphosphoric acid in 34% yield, to give β-(1-carboxy-1 : 2 : 3 : 4-tetrahydro-4-oxo-1-naphthyl)propionic acid (IV; R′ = CO_2H), which was characterized as the semicarbazone and the 2 : 4-dinitrophenylhydrazone of the half-ester. Esterification of carboxyl groups during the formation of dinitrophenylhydrazones has been previously reported by several workers (cf. Cowley and Schuette, *ibid.*, 1933, **55**, 3465; Strain, *ibid.*, 1935, **57**, 758; Ansell and Hey, *J.*, 1950, 2874; Reich, Crane, and Sanfilippo, *J. Org. Chem.*, 1953, **18**, 822.)

The cyclisation experiments with the α-methoxyphenylglutaric acids described in Part III (*loc. cit.*) and those recorded above with γ-carboxy-γ-phenylpimelic acid have given evidence of the deactivating influence of the nearer carboxyl group on the cyclisation process. This deactivation may be due to the fact that in the reaction medium the nearer carboxyl group would be converted into $-CO^+$. The γ-cyanopimelic acids now made available enable a comparative study to be made on the influence of the cyano-group in similar circumstances. Experiment has now shown that with (III; R = H, *m*-MeO, and *p*-MeO) cyclodehydration is effected readily with polyphosphoric acid at 100° in 70, 80, and 67% yield respectively. With the first two acids cyclodehydration is also effected with 95% sulphuric acid under mild conditions in 80 and 67% yield respectively, but with the *p*-methoxy-acid the use of sulphuric acid results in sulphonation. The ease with which the cyclodehydration of the γ-aryl-γ-cyanopimelic acids has been effected might suggest that, unlike the carboxyl group, the cyano-group does not change its structure in the reacting system, and become a positive pole.

The cyclisation product from γ-cyano-γ-*m*-methoxyphenylpimelic acid (III; R = *m*-MeO) can be β-(1-cyano-1 : 2 : 3 : 4-tetrahydro-7-methoxy-4-oxo-1-naphthyl)propionic acid (V) or its 5-methoxy-isomer, but oxidation of the product with sodium hypobromite to an oil, which on vacuum-sublimation gave 4-methoxyphthalic anhydride, confirmed its identity as a derivative of 6-methoxytetralone. The cyclisation of (III; R = H and *p*-MeO) offers no ambiguity and the products must be (IV; R′ = CN) and (VI) respectively, both of which were characterised as 2 : 4-dinitrophenylhydrazones. All attempts to effect the further cyclodehydration of the acid (IV; R′ = CN) and its 6- and 7-methoxy-derivatives were unsuccessful.

Experimental

γ-Cyano-γ-phenylpimelodinitrile, m. p. 70—71°, was prepared from benzyl cyanide and acrylonitrile by Bruson and Riener's method (*loc. cit.*) and hydrolysed with a mixture of sulphuric and acetic acids, to give γ-carboxy-γ-phenylpimelic acid, m. p. 153—154°, as described by Rubin and Wishinsky (*loc. cit.*).

γ-Cyano-γ-phenylpimelic Acid.—γ-Cyano-γ-phenylpimelodinitrile (1 g.) was boiled under reflux for 7 hr. with a solution of potassium hydroxide (1 g.) in a mixture of alcohol (2·5 c.c.) and water (2·5 c.c.). The alcohol was distilled off and water (10 c.c.) was added, followed by concentrated hydrochloric acid (20 c.c.). Ether extracted only a small quantity of oil (*ca.* 0·1 g.). The acid solution was evaporated almost to dryness and placed in the refrigerator for 24 hr. The precipitate was collected and washed with ice-cold water to remove sodium chloride. The insoluble residue on crystallisation from alcohol gave *γ-cyano-γ-phenylpimelic acid* (0·5 g.) in prisms, m. p. 168—170° (Found: C, 64·3; H, 5·6; N, 5·3. $C_{14}H_{15}O_4N$ requires C, 64·3; H, 5·7; N, 5·3%).

*γ-Cyano-γ-*m*-methoxyphenylpimelic Acid.*—A solution of acrylonitrile (4·9 c.c.) in *tert.*-butyl alcohol (5 c.c.) was added dropwise during 4½ hr. to a stirred solution of *m*-methoxybenzyl cyanide (5·3 g.) in *tert.*-butyl alcohol (10 c.c.) and 30% methanolic potassium hydroxide (1 c.c.) at 20—25°. After being stirred for 24 hr. at room temperature it was neutralised with dilute hydrochloric acid, diluted with ethyl alcohol (10 c.c.), and kept in the refrigerator for 2 days. The trinitrile which had separated was collected and crystallisation from alcohol gave *γ-cyano-γ-*m*-methoxyphenylpimelodinitrile* (7 g.) in prisms, m. p. 73—74° (Found: C, 70·9; H, 5·8. $C_{15}H_{15}ON_3$ requires C, 71·1; H, 5·9%). Hydrolysis of γ-cyano-γ-*m*-methoxyphenylpimelodinitrile (1 g.) with aqueous–alcoholic potassium hydroxide, as described above, gave *γ-cyano-γ-*m*-methoxyphenylpimelic acid* (0·5 g.), which separated from alcohol–light petroleum (b. p. 40—60°) as a microcrystalline powder, m. p. 159—161° (Found: C, 62·5; H, 5·7; N, 4·8. $C_{15}H_{17}O_5N$ requires C, 61·8; H, 5·8; N, 4·8%).

*γ-Cyano-γ-*p*-methoxyphenylpimelic Acid.*—In similar manner *p*-methoxybenzyl cyanide

(3·4 g.) and acrylonitrile (3 c.c.) gave *γ-cyano-γ-*p*-methoxyphenylpimelodinitrile* (4·0 g.), which separated from alcohol in prisms, m. p. 83—83·5° (Found: C, 71·3; H, 5·8; N, 16·8%). Hydrolysis of the trinitrile (1 g.) with aqueous-alcoholic potassium hydroxide, as described above, gave *γ-cyano-γ-*p*-methoxyphenylpimelic acid* (0·5 g.), which after crystallisation from alcohol melted at 156—158° after softening at 148° (Found: C, 61·2; H, 5·9; N, 4·75%).

Cyclisation of γ-Carboxy-γ-phenylpimelic Acid.—A solution of γ-carboxy-γ-phenylpimelic acid (2 g.) in 95% sulphuric acid (20 c.c.) was stirred for 30 min. at 0° and then for 4 hr. at room temperature. After being warmed for 5 min. on the steam-bath it was added to ice and extracted with ether. The extract was washed with aqueous sodium carbonate, the pink alkaline solution was acidified and extracted with ether, and the extract was washed with water and dried (Na_2SO_4). Evaporation left a yellow oil (1·4 g.), which solidified. Recrystallisation from ether–light petroleum (b. p. 40—60°) gave β-(1-*carboxy*-1 : 2 : 3 : 4-*tetrahydro*-4-*oxo*-1-*naphthyl*)*propionic acid* (0·8 g.), m. p. 167—168° (Found: C, 64·65; H, 5·65. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·35%). The *semicarbazone* crystallised from alcohol–pyridine in needles, m. p. 225° (decomp.) (Found: N, 12·7. $C_{15}H_{17}O_5N_3$ requires N, 13·15%). Treatment with 2 : 4-dinitrophenylhydrazine in concentrated sulphuric acid and alcohol (cf. Brady, *J.*, 1931, 756) gave the 2 : 4-*dinitrophenylhydrazone* of ethyl β-(1-carboxy-1 : 2 : 3 : 4-tetrahydro-4-oxo-1-naphthyl)propionate, which separated from benzene–ethyl acetate as a microcrystalline powder, m. p. 233—234° (Found: C, 55·8; H, 5·1; N, 11·5. $C_{22}H_{22}O_8N_4$ requires C, 56·1; H, 4·6; N, 11·9%). A similar cyclisation was effected in 34% yield by polyphosphoric acid at 100° for 1 hr. An attempt to effect the cyclisation through dehydrohalogenation of the acid chloride with (*a*) stannic chloride in benzene at 0° and (*b*) aluminium chloride in boiling carbon disulphide failed. With aluminium chloride in benzene (cf. Johnson and Glenn, *loc. cit.*) a neutral compound (2·5 g. from 5·6 g. of acid) was obtained in shining scales, m. p. 137—139° (from alcohol) (Found: C, 80·35; 81·1; H, 5·5; 6·0%). It gave a semicarbazone, m. p. 241—243° (crude), and a 2 : 4-dinitrophenylhydrazone, m. p. 233—235° after recrystallisation from chloroform–light petroleum (b. p. 40—60°).

Cyclisation of γ-Cyano-γ-phenylpimelic Acid.—By the method outlined above γ-cyano-γ-phenylpimelic acid (1 g.) and 95% sulphuric acid (10 c.c.) gave a white precipitate on decomposition with ice. Recrystallisation from alcohol gave β-(1-*cyano*-1 : 2 : 3 : 4-*tetrahydro*-4-*oxo*-1-*naphthyl*)*propionic acid* (0·75 g., 80%) in long needles, m. p. 200° (Found: C, 69·0; H, 5·3; N, 5·95. $C_{14}H_{13}O_3N$ requires C, 69·2; H, 5·35; N, 5·8%). A similar cyclisation was effected in 70% yield with polyphosphoric acid at 100° for 2 hr. The semicarbazone melted at 255° (decomp.), but because of its insolubility could not be recrystallised. The 2 : 4-*dinitrophenylhydrazone*, prepared by Brady's method, separated from nitrobenzene in orange crystals, m. p. 289—290° (Found: C, 56·7; H, 4·1. $C_{20}H_{17}O_6N_5$ requires C, 56·7; H, 4·0%). Attempts to effect cyclodehydrohalogenation of the acid chloride with (*a*) stannic chloride in benzene, (*b*) aluminium chloride in carbon disulphide, and (*c*) aluminium chloride in nitrobenzene, failed. Attempts to effect the further cyclodehydration of the 4-cyanopropionic acid with 95% sulphuric acid at 100° and 130° and polyphosphoric acid at 160° also failed.

*Cyclisation of γ-Cyano-γ-*m*-methoxyphenylpimelic Acid.*—γ-Cyano-γ-*m*-methoxyphenylpimelic acid (0·4 g.) in 95% sulphuric acid (4 c.c.) was stirred at 0° for 1 hr. and at room temperature for 2 hr., and then added to ice. Recrystallisation of the white precipitate from alcohol containing a little water gave β-(1-*cyano*-1 : 2 : 3 : 4-*tetrahydro*-7-*methoxy*-4-*oxo*-1-*naphthyl*)*propionic acid* (0·25 g., 67%) in small needles, m. p. 213—214° (Found: C, 65·6; H, 5·4; N, 5·1. $C_{15}H_{15}O_4N$ requires C, 65·9; H, 5·5; N, 5·1%). This acid was also obtained in 80% yield by cyclodehydration with polyphosphoric acid at 100° for 45 min. The 2 : 4-*dinitrophenylhydrazone*, prepared as above, separated from nitrobenzene in red crystals, m. p. 294° (decomp.) (Found: C, 55·4; H, 4·4; N, 15·0. $C_{21}H_{19}O_7N_5$ requires C, 55·6; H, 4·2; N, 15·45%). Attempted cyclodehydrohalogenation of the acid chloride with aluminium chloride, in both carbon disulphide and nitrobenzene, failed. Attempted further cyclodehydration of the 4-cyano-acid with polyphosphoric acid at 170° failed.

Oxidation of β-(1-*Cyano*-1 : 2 : 3 : 4-*tetrahydro*-7-*methoxy*-4-*oxo*-1-*naphthyl*)*propionic Acid* (cf. Ruzicka and Waldmann, *Helv. Chim. Acta*, 1932, **15**, 914).—The keto-acid (0·1 g.) was added to a solution of bromine (0·2 g.) in aqueous sodium hydroxide (0·6 g. in 10 c.c.), and the mixture warmed on the steam-bath for 15 min. and left at room temperature for 24 hr. The orange-coloured solution was decolorised with sulphur dioxide, further acidified with hydrochloric acid, and boiled to remove sulphur dioxide. When cold, the solution was extracted with ether. Evaporation of the solvent left a residue, which on sublimation at 180°/0·32 mm. gave 4-methoxyphthalic anhydride, m. p. 94°, both alone and on admixture with an authentic specimen prepared

from 6-methoxytetral-1-one by oxidation with potassium permanganate as described by Attwood, Stevenson, and Thorpe (*J.*, 1923, **123**, 1764).

Cyclisation of γ-Cyano-γ-p-methoxyphenylpimelic Acid.—γ-Cyano-γ-*p*-methoxyphenylpimelic acid (0·4 g.) was stirred with polyphosphoric acid (5 c.c.) for 1 hr. at 100° and the mixture was then added to ice. Crystallisation of the white precipitate from alcohol gave β-(1-*cyano*-1 : 2 : 3 : 4-*tetrahydro*-6-*methoxy*-4-*oxo*-1-*naphthyl*)*propionic acid* (0·25 g., 67%) in small needles, m. p. 213—214° (Found : C, 65·83; H, 6·05; N, 5·1. $C_{15}H_{15}O_4N$ requires C, 65·9; H, 5·5; N, 5·1%). The m. p. is identical with that of the corresponding 7-methoxy-compound : a mixed m. p. shows a big depression. The 2 : 4-*dinitrophenylhydrazone*, prepared as above, separated from nitrobenzene in orange crystals, m. p. 300—302° (Found : C, 55·7; H, 4·75; N, 15·4. $C_{21}H_{19}O_7N_5$ requires C, 55·6; H, 4·2; N, 15·45%). An attempted cyclodehydration with 95% sulphuric acid at room temperature gave a clear solution on addition to ice, probably owing to sulphonation. The further cyclodehydration of the cyano-acid with 95% sulphuric acid at room temperature and polyphosphoric acid at 150° failed.

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A Comparison of Chemical and Electrolytic Methods of Reduction.

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It is shown that there is a close relation between reduction by dissolving metals and electrolytic reduction, and that in favourable instances the rate of the former process can be predicted from electrolytic reduction data. This was confirmed experimentally for the reduction of a number of substances by zinc amalgam, zinc, and cadmium.

BY determining the yields of the various products obtained on the reduction of diene acids, Isaacs and Wilson (*J.*, 1936, 202, 574, 810; *Trans. Electrochem. Soc.*, 1939, **75**, 353) were able to distinguish two types of electro-reduction : (*A*) those at smooth cathodes, where reduction is similar to that by dissolving metals, and (*B*) those at cathodes of spongy nickel and of platinised platinum, where reduction is similar to catalytic hydrogenation. These conclusions are supported by the many isolated examples of such similarities that have been reported. The aim of this work is to provide a closer correlation of the two types of reducing systems in (*A*).

On the basis of the electrochemical theory of the corrosion of metals in conducting solutions the reaction

$$M + zH^+ \longrightarrow M^{z+} + \tfrac{z}{2}H_2$$

occurs as the result of two processes. At the anodic areas of the metal surface, the metal dissolves

$$M - ze \longrightarrow M^{z+}$$

and at the cathodic areas hydrogen ions are reduced

$$zH^+ + ze \longrightarrow \tfrac{z}{2}H_2$$

The hydrogen is formed by electrochemical action and the electrode potential of the cathodic areas is governed by the same factors as those which apply to the discharge of hydrogen at a normal cathode of the same material.

If a reducible substance (Ox) is added, the reaction is changed; some or all of the hydrogen ions previously liberated as molecular hydrogen react with the depolariser, *e.g.* :

$$Ox + nH^+ + ne \longrightarrow OxH_n$$

or $Ox + nH^+ + ne \longrightarrow Red + \tfrac{n}{2}H_2O$ where Red signifies the reduced form.*

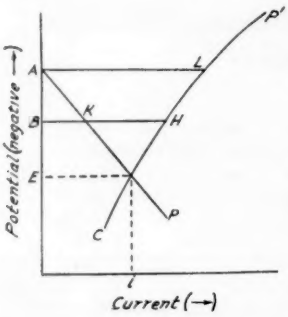
* The treatment given also applies to reduction reactions that can be formulated without hydrogen ions, *e.g.*, $Fe^{3+} + e \longrightarrow Fe^{2+}$.

The metal dissolves more rapidly than in the absence of the depolariser, but by the same process. The reduction of the depolariser takes place at cathodic areas, which may be different from those previously operating, while the reaction at the anodic areas remains the same.

On this basis, the reduction of a substance by dissolving metals in conducting solutions proceeds by electrochemical means, but no assumptions are made concerning the mechanism of electrolytic reduction. In the sections below, it is shown how the rate of chemical reduction may be predicted from purely electrolytic data, and the experimental work serves to test the conclusions reached. Two sets of conditions will be considered.

(I) *The Dissolving Metal has a Uniform Surface.*—The material studied, namely, liquid zinc amalgam, will be chosen as a specific example. Wagner and Traud (*Z. Elektrochem.*, 1938, **44**, 391) studied the reaction of zinc amalgam with acids and concluded that, although spatially separated anodic and cathodic areas do not exist on this material, an electrochemical mechanism of dissolution is still operative; almost the whole of the surface of the amalgam is acting as a cathode, and the anodic reaction is not restricted to any particular part of the surface, but occurs first at one point and then at another.

By obtaining values for the rate of reduction (I') and the cathode potential (e) for the electro-reduction of a given substance at zinc amalgam, it is possible, by an extrapolation of the e–log I' curve, to find the value of I' at the potential of the zinc amalgam when it is dissolving freely in the presence of the reducible substance. According to the argument presented above, this rate should be equal to the rate of chemical reduction.



In this instance, a simplification is possible. The overpotential behaviour of dilute liquid zinc amalgam is almost identical with that of pure mercury. Hence, the predicted rate of chemical reduction can be obtained from the appropriate e–log I' curve for mercury by interpolation.

This simplified procedure was used by Wagner and Traud for the reduction of hydrogen ions to molecular hydrogen, and good agreement between the predicted and the observed rates of chemical reduction was obtained. In the experimental section, this work is extended to the reduction of substances other than hydrogen ions, namely, maleic acid and potassium bromate.

(II) *The Dissolving Metal is Pure but its Surface is not Uniform.*—Dissolution of a pure solid metal may proceed to some extent by the mechanism indicated by Wagner and Traud but, because of the non-uniformity of the surface, spatially separated anodic and cathodic areas will also be operative. The cathodic areas will consist of portions of the metal that have a standard electrode potential and hydrogen overpotential *slightly* different from those of the metal in the anodic areas owing to differences in strain, crystal size, nature of crystal face exposed, etc.

The potential–current relations for such a system are represented graphically in the diagram (cf. Evans, " Metallic Corrosion, Passivity and Protection," Edward Arnold and Co., London, 1946, p. 256). It is assumed that metal ions are present in the solution when the potential of the metal is less negative than A, *i.e.*, when some " chemical " reduction is occurring, and that there are no metal ions present when the potential of the metal is more negative than A, *i.e.*, when the reduction is purely electrolytic. These conditions are those obtaining in the experimental work.

A–P represents the anodic polarisation curve; it may not be linear but for solutions that contain moderate quantities of simple metal ions the anodic polarisation is generally small. C–P' represents the cathodic polarisation curve.

When the metal is dissolving freely at a steady rate, the potentials of the anodic and the cathodic areas are equal * and given by E, and the current flowing (= rate of metal dissolution) is given by i.

* Strictly, these potentials differ by iR, where i is the current passing between the two types of area and R is the resistance offered by the solution; for good-conducting solutions, such as were used in the experimental work, iR is negligible.

If the metal is now cathodically polarised so that conditions represented by *B–K–H* are reached, the rate of metal dissolution has decreased to *B–K*. The cathodic current flowing is *B–H*, made up of *H–K*, the externally applied current and *B–K*, the internal current. When conditions represented by *A–L* are reached, metal dissolution ceases and the cathodic current *A–L* is equal to the externally applied current, *i.e.*, the cathodic reaction is purely electrolytic. It may be considered that, up to this stage, the cathodic reaction has taken place on the original cathodic areas only. If, however, the potential of the metal is made more negative than *A*, cathodic reaction will also occur on areas hitherto anodic, because these are of the same material as the cathodic areas and have hydrogen overpotentials that are only slightly different. This change-over may take place progressively as the potential is made more negative than *E*, but should be complete at potentials more negative than *A*. In these circumstances, the current distribution on the various parts of the electrode surface will not be quite regular, but the effect can be neglected.

By extrapolation of electrolytic reduction results, the value of I' at the potential E can be obtained. This rate should be greater than the observed rate of chemical reduction by a factor equal to

$$\frac{\text{effective area of the whole cathode}}{\text{effective area of the cathodic portions of the dissolving metal}}$$

Unfortunately, there are no methods of obtaining this ratio, but it will be near unity for metals where the anodic polarisation is small, *e.g.*, zinc and cadmium in simple salt solutions.

This treatment has been tested experimentally for the reduction of maleic acid, sodium hydrogen sulphite, and titanic sulphate, at electrodes of spectrographically pure zinc and cadmium.

Experimental

Apparatus.—The reduction cell was constructed so that the anolyte and catholyte were prevented from mixing, and atmospheric oxygen was excluded. It consisted of an H-shaped vessel of Pyrex glass. The two vertical compartments, which held the anode and the cathode, were connected at their lower ends by a water-sealed tap that was kept closed during electrolysis. The cathode compartment, which had a volume of ~150 ml., was fitted with a water-sealed ground-glass cap, into which were sealed two narrow vertical tubes. These were ground to receive two sliding tubes that carried the electrode and a Luggin capillary; thus the electrode could be lowered into or raised from the solution and the capillary tip could be moved over the surface of the electrode without disturbing the rest of the apparatus. (Suitable modifications were made for experiments with liquid cathodes.) A burette was also sealed through the cap of the cathode compartment and a separate inlet tube for further reagents was provided so that, when necessary, titration of the solution after reduction could be carried out without opening the cell to the atmosphere. Stirring was effected by a stream of hydrogen, which entered at the bottom of the compartment and emerged through a " bubbler " above the level of the solution. The anode compartment was fitted with a ground-glass cap that carried the platinum anode. Gaseous anodic products were swept out of the anolyte by a stream of hydrogen.

The cell was immersed in a water-bath maintained at 25° ± 0·1°.

Electrodes.—The zinc and cadmium were " spectrographically standardised " rods supplied by Johnson, Matthey and Co., Ltd. Before use, the electrodes were rubbed with fine glass-paper, washed with conductivity water, etched in 5N-hydrochloric acid for 5 min., washed again with conductivity water, and finally kept in a sample of the solution to be studied until required. Mercury was distilled twice and finally purified by Brummer and Náray-Szabó's method (*Z. Elektrochem.*, 1925, **31**, 95).

Reagents, Analysis, etc.—All solutions were prepared with conductivity water. 0·1N-Solutions of the reducible compounds were prepared in one of three supporting electrolytes; (I) N-acetic acid–N-sodium acetate; (II) N-sulphuric acid; (III) N-potassium chloride.

Maleic acid solutions were prepared from maleic anhydride that had been crystallised from chloroform. Maleic acid was determined by Lucas and Pressman's method (*Ind. Eng. Chem. Anal.*, 1938, **10**, 140). Potassium bromate was determined iodometrically. The sodium hydrosulphite (dithionite) formed by the reduction of sodium hydrogen sulphite was determined by

Merriman's method (*J. Soc. Chem. Ind.*, 1923, **42**, 290). Titanic sulphate solutions were prepared by the decomposition of recrystallised potassium titanyl oxalate with sulphuric acid, followed by suitable dilution. The tervalent titanium formed on reduction was determined by adding ferric alum and titrating the resultant ferrous iron with 0·1N-potassium permanganate.

The presence of the reduction products had no effect on the rate of reduction at a given potential. In some of the chemical reductions, sufficient of the appropriate metal salt was added to give an approximately 0·1M-solution. The potential of the dissolving metal was, however, stable without this addition.

Hydrogen used for stirring was passed over palladised asbestos at 350° to remove the bulk of the oxygen; after being cooled, it was passed through a sample of the solution in use and thence to the cell.

Electrical Measurements.—Current densities of between 10^{-4} and 5×10^{-2} amp./sq. cm. and electrode areas of between 20 and 1 sq. cm. were employed. The Luggin capillary was connected either to a hydrogen electrode dipping into a sample of the supporting electrolyte or to a normal calomel electrode. The e.m.f. of the cell cathode–reference electrode was measured to the nearest mv. Thus the cathode potential was determined as in the direct method for the determination of hydrogen overpotential.

General Procedure.—100 Ml. of the solution were placed in the cathode chamber, and ~50 ml. of the same solution in the anode chamber. The prepared cathode was placed in position above the solution, and assembly of the cell completed. After hydrogen had been passed through both compartments for 1 hr., the polarising source was switched on and the cathode lowered into the electrolyte. The current was immediately adjusted and electrolysis was allowed to proceed until approx. 10% of the depolariser had been reduced. During the electrolysis, the cathode potential was determined at frequent intervals. At the end of the electrolysis the cathode was raised from the electrolyte, and the polarising source switched off. Analysis of the reduced solution was then carried out on a suitable aliquot portion or, when necessary, *in situ*. Chemical reductions were carried out by similar means but without polarisation of the electrode or use of the anode chamber.

Results

The cathode potential (e) rapidly attained a maximum negative value and then remained constant to within ±0·01 v over a period of hours. The mean value of e was taken in each case. The relation between e and the rate of reduction (I') of a given substance was of the form $-e = a + b' \log I'$ where a and b' are constants. The value of b' was in most cases about 0·1.

The predicted rates of chemical reduction, by zinc amalgam, of maleic acid and of potassium bromate were obtained by interpolation from the appropriate e–log I' lines for a mercury cathode. The predicted rates of chemical reduction for the other systems were obtained by extrapolation of the e–log I' lines for zinc and cadmium cathodes.

In the Tables below, the supporting electrolyte is indicated by the appropriate Roman numeral; i is the total current in milliamp.; A is the area of the cathode in sq. cm.; I is the cathodic current density in amp./sq. cm.; t is the time of electrolysis in hours; B is the amount of reduction in milliequivs.; and I' is the rate of reduction expressed as amp./sq. cm. The cathode potential, e, is expressed in mv relative to the reversible hydrogen-electrode potential in the supporting electrolyte used, except for the reductions of sodium hydrogen sulphite, where the cathode potential is on the hydrogen scale.

The values given represent the mean of duplicates in most cases; in duplicate experiments the cathode potentials observed for a given rate of reduction did not differ by more than 0·015 v. The difference between the logarithms of the predicted and the observed rates of reduction does not exceed 0·1, and this is therefore within the limits of experimental error.

Discussion

The results, although limited in number, cover a range of rates of reduction and offer a verification of the treatment given. Reduction by dissolving metals in conducting solutions proceeds by electrochemical means but no assumptions have been made concerning the mechanism of electrolytic reduction.

Reduction by dissolving metals is usually, but not universally, regarded as taking place by successive addition of hydrogen ions and electrons to the reducible substance, whereas electro-reduction is frequently ascribed to the direct action of hydrogen atoms. The

mechanism of both processes is, however, the same. If an " atomic hydrogen " theory of hydrogen overpotential is accepted, electroreduction must occur by reaction of the depolariser with atomic hydrogen. If a " slow discharge " theory of hydrogen overpotential is accepted, a mechanism of electroreduction based on the successive addition of

i	A	$10^4 I$	$-e$	t	B	I'
(a) *Zinc amalgam electrodes.*						
			Reduction of maleic acid (I)			
30·4	1	304	607	—	—	*
9·7	1	97	510	—	—	*
3·05	1	30·5	467	—	—	*
0·97	1	9·7	437	—	—	*
0	1	0	550	1	0·56	$1·5 \times 10^{-2}$
						Predicted $1·8 \times 10^{-2}$
			Reduction of potassium bromate (I)			
1·36	1	13·6	747	3	0·15	$1·34 \times 10^{-3}$
3·03	1	30·3	785	—	—	*
0·98	1	9·8	734	—	—	*
0·097	1	0·97	625	—	—	*
0·0302	1	0·302	561	—	—	*
0·0096	1	0·096	508	—	—	*
0	12·56	0	556	38	0·50	$2·8 \times 10^{-5}$
						Predicted $2·6 \times 10^{-5}$
(b) *Zinc electrodes.*						
			Reduction of sodium hydrogen sulphite (III)			
40	4	100	1013	1·5	0·90	$4·03 \times 10^{-3}$
12	4	30	906	2	0·87	$2·91 \times 10^{-3}$
4	4	10	849	2	0·75	$2·51 \times 10^{-3}$
0	4	0	831	2	0·69	$2·3 \times 10^{-3}$
						Predicted $2·4 \times 10^{-3}$
			Reduction of maleic acid (I)			
4·7	1·14	42	580	1	0·94	$2·21 \times 10^{-2}$
0·46	1·14	4·2	558	1	0·78	$1·83 \times 10^{-2}$
0	1·14	0	545	1	0·77	$1·8 \times 10^{-2}$
						Predicted $1·6 \times 10^{-2}$
			Reduction of titanic sulphate (II)			
34	3·38	100	789	1	0·83	$6·58 \times 10^{-3}$
3·4	3·38	10	776	1	0·63	$5·0 \times 10^{-3}$
0·28	2·77	1	766	2	0·91	$4·4 \times 10^{-3}$
0	1·64	0	761	1·5	0·39	$4·3 \times 10^{-3}$
						Predicted $3·9 \times 10^{-3}$
(c) *Cadmium electrodes.*						
			Reduction of sodium hydrogen sulphite (III)			
12	4	30	770	1·5	0·61	$2·73 \times 10^{-3}$
4	4	10	630	2	0·38	$1·27 \times 10^{-3}$
0·4	4	1	549	2	0·31	$1·04 \times 10^{-3}$
0	4	0	539	2	0·36	$1·2 \times 10^{-3}$
						Predicted $1·0 \times 10^{-3}$
			Reduction of maleic acid (I)			
4·5	5	9	452	4	0·65	$8·72 \times 10^{-4}$
1·25	5	2·5	377	5	0·25	$2·68 \times 10^{-4}$
0·35	11·5	0·3	327	23	1·25	$1·27 \times 10^{-4}$
0	11·5	0	300	24	1·03	$1·0 \times 10^{-4}$
						Predicted $0·8 \times 10^{-4}$
			Reduction of titanic sulphate (II)			
25	2·5	100	976	1	0·36	$3·86 \times 10^{-3}$
4·7	4·66	10	461	1	0·68	$3·91 \times 10^{-3}$
0·47	4·66	1	458	1	0·67	$3·85 \times 10^{-3}$
0	4·66	0	451	1	0·66	$3·8 \times 10^{-3}$ †
						Predicted $3·8 \times 10^{-3}$

* Comparison of e with the hydrogen overpotential of mercury at the same c.d. in the supporting electrolyte showed that depolarisation was very large and therefore it could be assumed that $I' = I$. In these experiments, i was measured with a specially calibrated microammeter.

† Clearly, I' is limited by the rate of diffusion of depolariser to the cathode under the conditions used.

hydrogen ions and electrons to the depolariser seems more feasible than the direct addition of atomic hydrogen as usually postulated.

The prediction of the rate of chemical reduction from electroreduction data can only be made when the nature and the extent of the cathodic areas of the dissolving metal are known, *e.g.*, when the dissolving metal is pure and shows low anodic polarisation or when a metallic couple is being used. It is intended to present later an account of the reduction behaviour of metallic couples and also to extend the present comparison to group *B* reducing systems.

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Co-ordination Compounds of Boron Trihalides. Part II. Boron Trichloride–Cyclic Ethers.*

By JOAN GRIMLEY and A. K. HOLLIDAY.

[Reprint Order No. 4771.]

Boron trichloride forms 1 : 1 compounds with ethylene oxide, propylene oxide, tetrahydrofuran, and tetrahydropyran. Ethylene oxide–boron trichloride dissociates reversibly on heating; the other 1 : 1 compounds yield boron trichloride and hydrogen chloride in amounts depending upon the ring size.

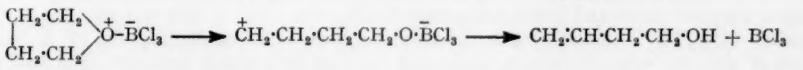
IN Part I * the compound of boron trichloride with dioxan was described, and we now report the preparation and properties of some cyclic ether–boron trichloride co-ordination compounds.

The 1 : 1 compounds of boron trichloride with ethylene oxide, propylene oxide, tetrahydrofuran, and tetrahydropyran fume strongly in moist air and react spontaneously with water, forming boric acid and liberating hydrogen chloride. When these compounds are heated they may decompose in one or more of three ways, *viz.*: (*a*) by simple breaking of the boron–oxygen bond, *i.e.*, dissociation; (*b*) by ring fission followed by loss of boron trichloride; (*c*) by ring fission followed by loss of hydrogen chloride. Ethylene oxide–boron trichloride decomposes reversibly by process (*a*) only. This compound appears to be dimeric in the vapour state at low temperatures, dissociating into monomer and thence into ethylene oxide and boron trichloride at higher temperatures. Propylene oxide–boron trichloride decomposes irreversibly on heating, and at 100° the decomposition products include boron trichloride and hydrogen chloride in the molar ratio 3 : 1, a colourless volatile liquid of empirical formula $(C_3H_6O)_2BCl_3$, and a non-volatile residue containing boron and chlorine (B : Cl = 1 : 0·77). With the reasonable assumption that $(C_3H_6O)_2BCl_3$ is the molecular formula of the liquid condensate, the primary decomposition is then by mechanism (*a*), *e.g.*, $2C_3H_6\overset{+}{O}\text{–}\overset{-}{B}Cl_3 \longrightarrow (C_3H_6O)_2BCl_3 + BCl_3$; some secondary decomposition by mechanisms (*b*) and (*c*) must also take place. The compound $(C_3H_6O)_2BCl_3$ reacted vigorously with water to yield hydrogen chloride and boric acid in solution, but was not investigated further. This compound could also be formulated as the chloroboronate $[CH_2Cl{\cdot}CH(CH_3)O]_2BCl$. Martin and Mako (*J. Amer. Chem. Soc.*, 1951, **73**, 2674) have shown that β-substitution by chlorine for hydrogen in chloroboronates would be expected to weaken the boron–oxygen bond.

Tetrahydrofuran–boron trichloride decomposes irreversibly between 38° and 52°; at 87° boron trichloride and hydrogen chloride are recovered in the molar ratio 4·8 : 1,

* The paper by Holliday and Sowler, *J.*, 1952, 11, is regarded as Part I of this series.

together with a colourless volatile liquid which contains effectively no boron or chlorine and behaves as a pure substance, b. p. 112°/760 mm. (by extrapolation). If mechanism (*b*) is postulated for the primary decomposition, then a plausible scheme is



forming but-3-enol (b. p. 112·5—113·5°). Saturated alcohols react readily with boron trichloride to form boric esters (Wiberg and Sütterlin, *Z. anorg. Chem.*, 1931, **202**, 1; Gerrard and Lappert, *J.*, 1951, 2545), but unsaturated alcohols have not been investigated. The only other C_4H_8O compound having b. p. ~112° is 2-methylallyl alcohol (b. p. 114°).

Tetrahydropyran–boron trichloride melts with decomposition at 52°. A sample heated at 90° for several hours yields only hydrogen chloride and an unidentified liquid containing boron and chlorine in the ratio 1 : 2. The amount of hydrogen chloride recovered corresponded to the loss of one chlorine atom from three molecules of the 1 : 1 compound. This suggests decomposition by mechanism (*c*), *i.e.*, $C_5H_{10}\overset{+}{O}\text{–}\overset{-}{B}Cl_3 \longrightarrow C_5H_9O{\cdot}BCl_2 + HCl$, but the condensate is too low in boron and chlorine to be the chloroboronite, $C_5H_9O{\cdot}BCl_2$.

It is observed that as the ring size of the donor molecule increases, (i) the temperature of decomposition rises, and (ii) the amount of boron trichloride isolated after thermal decomposition falls, and the amount of hydrogen chloride increases. Again, α-substitution in the ethylene oxide ring by a methyl group for a carbon-attached hydrogen, or replacement of a ring CH_2 group in tetrahydropyran by an oxygen atom has the same effects as an increase in ring size; *e.g.*, dioxan–boron trichloride melts with decomposition at 78°, and at 80°, 0·97 mmole of hydrogen chloride is recovered from each mmole of the 1 : 1 compound (Part I, *loc. cit.*). Although it is not possible to determine unequivocally an order of stability for the boron trichloride–cyclic ethers, the tentative orders ethylene oxide>propylene oxide, and dioxan>tetrahydropyran>tetrahydrofuran are proposed, based on the temperature of initial decomposition of the 1 : 1 compounds and on the nature of the thermal decomposition products. These orders may be compared with the electron-donor abilities of cyclic ethers in hydrogen bonding, determined by Searles, Tamres, and Lippincott (*J. Amer. Chem. Soc.*, 1953, **75**, 2775). They measured the heats of mixing of ethylene oxide, propylene oxide, tetrahydrofuran, and tetrahydropyran with chloroform, and found an order propylene oxide>ethylene oxide, and tetrahydrofuran> tetrahydropyran>ethylene oxide. Hamilton, McBeth, Bekebrede, and Sisler (*ibid.*, p. 2881) also found an order of stability, dioxan>(tetrahydrofuran, tetrahydropyran) for 1 : 1 compounds of these donors with titanium tetrachloride.

Tetrahydropyran–boron trichloride and dioxan–boron trichloride both react with equimolar amounts of hydrogen chloride at low temperatures; the resulting compounds can be given the ionic formulations $[C_5H_{10}{\cdot}OH]^+[BCl_4]^-$ and $[O<(CH_2{\cdot}CH_2)_2>OH]^+[BCl_4]^-$. There is some evidence that other 1 : 1 addition compounds of boron trichloride do add on hydrogen chloride to form ionic borochlorides (Hewitt and Holliday, *J.*, 1953, 530).

Experimental

The addition compounds were prepared in a general-purpose high-vacuum apparatus similar to that described by Sanderson ("Vacuum Manipulation of Volatile Compounds," Wiley, New York, 1948). Transfers of non-volatile, moisture-sensitive materials were made in a dry box. The methods used for the analysis of boron and chlorine, and the apparatus used to determine molecular weights in solution, were as described in Part I (*loc. cit.*). Vapour-pressure measurements were made by means of Stock and Küss's isoteniscope method (*Ber.*, 1914, **47**, 3115). Volatile starting materials were purified by fractionation in the high-vacuum apparatus; less volatile materials were dried and then fractionally distilled.

Reaction of Boron Trichloride and Ethylene Oxide.—Equivalent amounts (2·34 mmoles) of ethylene oxide (v. p. 3·5 mm. at −78·5°) and boron trichloride (v. p. 3—4 mm. at −78·5°) were mixed at −78·5°. Reaction was spontaneous, and a colourless liquid containing a small

amount of white solid was formed. Distillation *in vacuo* at 20° gave 0·158 g. (0·98 mmole) of liquid, *ethylene oxide–boron trichloride* (Found: B, 6·4; Cl, 65·1%; *M*, 165. C_2H_4O,BCl_3 requires B, 6·8; Cl, 66·0%; *M*, 161). The only other products were 0·67 mmole of boron trichloride and 0·14 mmole of hydrogen chloride. The highly viscous non-volatile residue contained ethylene oxide and boron trichloride in the ratio 1·97 : 1, but was not dioxan–boron trichloride, m. p. 78°. Ascending and descending vapour-pressure readings for 10° increments between 0° and 90° were coincident, indicating that no irreversible decomposition had taken place over this range. Saturated vapour-pressure data are given by $\log p + 1263/T = 5{\cdot}90$, hence the apparent boiling point is 146° at 760 mm. (extrap.), the molar latent heat (20—90°) is 5·78 kcal./mole, and Trouton's constant is 13·8. Vapour densities over the range 18—118° were determined by measuring the pressure exerted by a known weight of the compound in a high-temperature bulb (Sanderson *loc. cit.*); the results are given below:

Temp.	18·0°	37·3°	44·1°	56·1°	68·0°	81·3°	98·0°	118·0°
V.d.	153·5	124·2	112·2	90·0	79·2	73·5	71·5	69·5

The calculated vapour density for C_2H_4O,BCl_3 is 80·7.

Reaction of Boron Trichloride and Propylene Oxide.—Propylene oxide (4·75 mmoles, v. p. 183 mm. at 0°) and boron trichloride (4·80 mmoles) were mixed at −78·5°. A colourless liquid was formed which became yellow when warmed to room temperature; distillation *in vacuo* at 20° yielded 0·696 g. (3·98 mmoles) of *propylene oxide–boron trichloride* as a colourless liquid (Found: B, 5·88; Cl, 61·1%; *M*, 177. C_3H_6O,BCl_3 requires B, 6·16; Cl, 60·7%; *M*, 175). The only other volatile product was hydrogen chloride (0·22 mmole), and the non-volatile residue contained propylene oxide and boron trichloride in the ratio 1·0 : 1·07. Non-reproducibility of saturated vapour-pressure readings between 0° and 60° indicated that irreversible decomposition had taken place throughout this temperature range. A freshly distilled sample (3·97 mmoles) was heated at 102° for 1 hr.; 0·59 mmole of hydrogen chloride and 1·16 mmoles of boron trichloride were formed, together with 0·1 g. of a colourless liquid which condensed out at −78·5° [Found: B, 4·30; Cl, 45·2. $(C_3H_6O)_2BCl_3$ requires B, 4·64; Cl, 45·8%] and 0·07 g. of a brown, non-volatile residue (Found: B, 11·4; Cl, 28·6%).

Reaction of Boron Trichloride and Tetrahydrofuran.—When the liquid reactants were mixed at −78·5°, the reaction was strongly exothermic and gave an ill-defined product. The 1 : 1 compound was isolated, however, when equivalent amounts (10·4 mmoles) of tetrahydrofuran (b. p. 65·2—66°/760 mm.) and boron trichloride were condensed separately into the limbs *A* and *B* of a reaction vessel, and the whole was immersed in a bath at −78·5° for 12 hr. Volatile products at 20° were then condensed into *B*, and tube *A*, which contained a white solid, was sealed off from *B* and later opened in the dry box and analysed (Found: B, 5·80; Cl, 54·4%; *M*, 185. C_4H_8O,BCl_3 requires B, 5·72; Cl, 56·2%; *M*, 189). Thus, 10 mmoles of *tetrahydrofuran–boron trichloride* were formed in *A*. The volatile products in *B* were identified as tetrahydrofuran (0·18 mmole) and hydrogen chloride (0·69 mmole). Saturated vapour-pressure measurements were made on a sample of the 1 : 1 compound prepared directly in the isoteniscope. The compound melted slowly, with decomposition, between 38° and 52°; an abrupt discontinuity in the vapour pressure–temperature curve occurred at the latter temperature, and a clear cherry-red liquid was seen in the isoteniscope. On cooling below 52°, no solid separated and vapour-pressure values remained high, *i.e.*, irreversible decomposition had occurred. A freshly prepared sample was heated for 2 hr. at 60° and then for a further 2 hr. at 87°; the decomposition products included boron trichloride, hydrogen chloride, and a colourless liquid which condensed at −78·5° and contained only traces of boron and chlorine. Saturated vapour pressures of the latter compound followed the equation $\log p + 1720/T = 7{\cdot}35$, giving b. p. = 112° at 760 mm. (extrapolated).

Reaction of Boron Trichloride and Tetrahydropyran.—Boron trichloride (15·8 mmoles) was bubbled through excess of tetrahydropyran (b. p. 87—87·8°/760 mm.) at −40°. Volatile products were distilled off at 20°, and tetrahydropyran alone was isolated. The white solid remaining in the reaction vessel was sublimed *in vacuo* below 52°; needle-shaped crystals separated and were identified as *tetrahydropyran–boron trichloride* (14·2 mmoles) (Found: B, 5·50; Cl, 52·1%; *M*, 203. $C_5H_{10}O,BCl_3$ requires B, 5·40; Cl, 52·3%; *M*, 203·5). It melts slowly, with decomposition, between 49° and 52°, and at the latter temperature there is a marked discontinuity in the saturated v. p.–temperature curve, and, on cooling, vapour-pressure values are not reproduced, indicating irreversible decomposition. Freshly prepared samples were therefore heated in sealed tubes at 90° for different periods of time. The only products isolated were hydrogen chloride and a colourless liquid condensate at −78·5° (Found:

B, 3·0; Cl, 18·9%). The following table shows the effect of the time of heating on the amount of hydrogen chloride produced.

Time of heating, hr.	3	5	25
$C_5H_{10}O,BCl_3$: HCl	1 : 0·19	1 : 0·29	1 : 0·33

Reaction of Tetrahydropyran–Boron Trichloride with Hydrogen Chloride.—Excess of dry hydrogen chloride (41·0 mmoles) was condensed on solid, freshly-prepared tetrahydropyran–boron trichloride (5·47 mmoles) at −196°, and the temperature allowed to rise to −112°. The tube was shaken vigorously, and reaction allowed to take place for 2 hr.; the 1 : 1-compound dissolved when shaken. Unchanged hydrogen chloride was then distilled off (at −112°) until the vapour pressure fell from 122 mm. (for hydrogen chloride) to a persistently low value of 66 mm.; 35·3 mmoles of hydrogen chloride were then recovered. On warming to 20°, the remaining 5·70 mmoles of hydrogen chloride were evolved. Hence, if the compound $C_5H_{10}O,BCl_3,HCl$ is formed at −112°, it dissociates completely above this temperature into hydrogen chloride and tetrahydropyran–boron trichloride.

Reaction of Dioxan–Boron Trichloride with Hydrogen Chloride.—Excess of dry hydrogen chloride (46·1 mmoles) was condensed on solid dioxan–boron trichloride (7·97 mmoles) at −196°, and the temperature allowed to rise to −112°. The solid did not dissolve at this temperature, even after vigorous shaking. After 2 hours' reaction at −112°, 40·3 mmoles of hydrogen chloride were recovered, and the vapour pressure above the solid fell to 31 mm. On warming to 20°, the remaining 5·80 mmoles of hydrogen chloride were recovered. Thus, if a compound is formed between hydrogen chloride and dioxan–boron trichloride at −112°, it dissociates completely above this temperature.

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Co-ordination Compounds of Boron Trihalides. Part III. Compounds of Boron Trifluoride with Cyclic Ethers and Dioxan.*

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Boron trifluoride forms 1 : 1 compounds with propylene oxide and tetrahydropyran; evidence for the existence of ethylene oxide–boron trifluoride below −78·5° has been obtained. Boron trifluoride also reacts with dioxan to form the compounds $C_4H_8O_2$, BF_3 and $C_4H_8O_2,2BF_3$.

A FEW addition compounds of boron trifluoride with cyclic ethers have been reported previously. Brown and Adams (*J. Amer. Chem. Soc.*, 1942, **64**, 2557) investigated tetrahydrofuran–boron trifluoride as one of a series of 1 : 1 ether–boron trifluoride compounds, and found tetrahydrofuran to be a stronger donor than dimethyl, diethyl or di*iso*propyl ether. The heat of dissociation of tetrahydrofuran–boron trifluoride was given as 13·4 kcal. Stone and Emeléus (*J.*, 1950, 2755), using a large excess of ethylene oxide, studied the reaction of boron trifluoride with ethylene oxide; it was highly exothermic, and dioxan and a liquid polymeric boron-containing material were formed; the latter depolymerised at room temperature to give more dioxan and an unidentified, less volatile material. Schmeisser and Jenkner studied this reaction more recently (*Z. Naturforsch.*, 1952, **76**, 583) but also failed to isolate the 1 : 1 compound C_2H_4O,BF_3; even at low temperatures white crystals of dioxan–di(boron trifluoride) were formed, which decomposed at 130° into dioxan and boron trifluoride. Greenwood and Martin (*J.*, 1951, 1915) reported the formation of a stable addition compound of boron trifluoride with dioxan. The compounds $C_4H_8O_2,BF_3,2H_2O$ and $C_4H_8O_2,BF_3,H_2O$ were prepared by Meerwein and Pannwitz (*J. pr. Chem.*, 1934, **141**, 123) by the interaction of dioxan and the appropriate hydrate of boron trifluoride.

The reactions of boron trifluoride with ethylene oxide, propylene oxide, tetrahydropyran, and dioxan are now described. When ethylene oxide is condensed on to a considerable

* Part II, preceding paper.

excess of boron trifluoride at −196° and the reaction temperature is kept below −78·5°, approximately equimolar quantities of the two react to form a white solid which is probably the 1 : 1 compound. On warming to 20°, this compound rapidly darkens; considerable heat is developed, droplets of a non-volatile liquid are formed, and boron trifluoride is evolved. When, however, equivalent amounts of ethylene oxide and boron trifluoride react at −78·5° there is formed a mixture of brown and white solids which rapidly changes to a purple liquid when warmed to 20°. Boron trifluoride is recovered from this mixture on re-cooling to −78·5°, and dioxan is identified at 20°. Since dioxan and boron trifluoride form solid addition compounds of negligible volatility at −78·5°, dioxan could not have been present at −78·5° when boron trifluoride was recovered, but must have been formed on rewarming to 20°.

Equimolar amounts of propylene oxide and boron trifluoride react at −112° to give a red, viscous, non-volatile liquid, stable at room temperature. The extremely low volatility of this (presumably) 1 : 1 compound precluded further purification in the vacuum-system, and no other physical properties were determined.

Tetrahydropyran and boron trifluoride form a stable 1 : 1-compound which dissociates reversibly when heated above 80°; the heat of dissociation is approximately 38 kcal. The heat of dissociation of tetrahydrofuran–boron trifluoride (Brown and Adams, *loc. cit.*) is much less (13·4 kcal.).

The 1 : 1 compound dioxan–boron trifluoride is prepared by direct addition; on sublimation *in vacuo* at 50—60° it yields a sublimate consisting of dioxan–di(boron trifluoride) and dioxan: $2C_4H_8O_2,BF_3 \longrightarrow C_4H_8O_2,2BF_3 + C_4H_8O_2$. The 1 : 2 compound is also prepared by the reaction of liquid boron trifluoride on the 1 : 1-compound at −112°. Both the 1 : 1 and the 1 : 2 compound are only sparingly soluble in benzene and light petroleum, but appreciably soluble in dioxan. Cryoscopic determinations of the molecular weight for dioxan–boron trichloride in dioxan as solvent gave normal values (Holliday and Sowler, *J.*, 1952, 11), yet the apparent molecular weights of both the dioxan–boron trifluoride compounds are abnormally high in this solvent, and decrease with increasing solute concentration. The expected values for monomeric 1 : 1 and 1 : 2 compounds are only approached at high solute concentrations. The cryoscopic solutions were too sensitive to moisture to permit analysis of the crystals obtained on freezing. Since the 1 : 1 compound is found to react with water to form the dihydrate $C_4H_8O_2,BF_3,2H_2O$ (m. p. 140°), previously obtained by Meerwein and Pannwitz (*loc. cit.*), it seems probable that dioxan molecules may also add on when either the 1 : 1 or the 1 : 2 compound is dissolved in dioxan. Formation of aggregates of the type $(dioxan)_n$–boron trifluoride would account for the high molecular weights observed in dilute solution, and with increasing solute concentration n might reasonably be expected to fall, giving the observed decrease in molecular weight.

The 1 : 1 compound melts over the range 91·4—96·1°, with a small amount of irreversible decomposition. The 1 : 2 compound does not melt below 117°; saturated vapour-pressure measurements for this compound are reproducible between 25° and 117°. The 1 : 1 compound undoubtedly dissociated when heated to give dioxan and boron trifluoride, but in view of the low value of the saturated vapour pressure of this compound at relatively high temperatures (*e.g.*, 17 mm. at 75°), no measurements of the dissociation constant were attempted. It seems clear that dioxan–di(boron trifluoride) is more stable than the 1 : 1 compound, since it is formed when the latter is heated in an open system.

The stability of cyclic ether–boron trifluoride compounds appears to increase with increase of ring size, as was observed in the boron trichloride–cyclic ether series (Part II, *loc. cit.*). The increase in stability observed in passing from ethylene oxide–boron trifluoride to tetrahydropyran–boron trifluoride is much more marked than the corresponding transition in the boron trichloride series. Again, the introduction of a methyl group into ethylene oxide, to form propylene oxide, has a different effect, since propylene oxide–boron trifluoride is certainly more stable than ethylene oxide–boron trifluoride. Replacement of a ring methylene group in tetrahydropyran by an oxygen atom, to form dioxan, increased the thermal stability of the boron trichloride addition compound, but this effect is not so obvious in the case of the boron trifluoride addition compounds, as the stability is already large. The most marked difference between the two sets of compounds is the complete

absence of decomposition of the boron trifluoride addition compounds by ring fission, followed by elimination of hydrogen fluoride. This can doubtless be ascribed to the different effects of the two boron trihalides on the ring atoms, leading to differences in the ease with which carbon-attached hydrogen atoms can be attacked. Certainly there is a notable difference in the effect of single co-ordination to the dioxan ring, in that a 1 : 2 compound with *two* co-ordinated boron trihalide molecules can be made from the 1 : 1 compound for the trifluoride but not for the trichloride. This does not necessarily imply a marked difference in the character of the unco-ordinated oxygen atoms of dioxan–boron trifluoride and dioxan–boron trichloride, as non-formation of dioxan–di(boron trichloride) may be explained equally well in terms of the difference in " co-ordinating power " or electronegativity of the two trihalides. A study of oxygen-containing rings with *both* boron trifluoride and boron trichloride co-ordinated simultaneously is now in progress.

Experimental

The experimental methods were as described by Holliday and Sowler (*J.*, 1952, 11). Boron trifluoride was estimated volumetrically by the method of Swinehart, Bumblis, and Flisik (*Analyt. Chem.*, 1947, **19**, 28). As an additional check fluoride was estimated gravimetrically as calcium fluoride, and boron was determined in the filtrate.

Commercial boron trifluoride was purified by fractionation in a high-vacuum apparatus, and then stored in a mercury-sealed bulb.

Reaction of Boron Trifluoride with Ethylene Oxide.—Ethylene oxide (5·6 mmoles) was condensed on to excess (34·7 mmoles) of boron trifluoride (v. p. 292 mm. at −111·8°) at liquid-nitrogen temperature. After 3 hr. at −111·8°, a white solid remained at the bottom of the reaction vessel and a brown residue at the top. 28·1 mmoles of unchanged boron trifluoride were recovered at −111·8°; hence 6·6 mmoles had reacted with the ethylene oxide (ratio $C_2H_4O : BF_3 = 1 : 1·18$). When the vessel was warmed to −78·5°, 2·0 mmoles of boron trifluoride were evolved, and the white solid became discoloured (ratio $C_2H_4O : BF_3 = 1 : 0·82$). When the temperature rose to that of the room only boron trifluoride (1·1 mmoles) was isolated.

Reaction of Boron Trifluoride with Propylene Oxide.—Propylene oxide (6·3 mmoles) was condensed on boron trifluoride (34·8 mmoles) at liquid-nitrogen temperature. Warming to −111·8° produced dense brown fumes; after 30 min. at this temperature, excess of boron trifluoride (28·4 mmoles) was recovered. No further evolution of boron trifluoride occurred when warmed to 20°. Hence 6·4 mmoles of boron trifluoride react with 6·3 mmoles of propylene oxide.

Reaction of Boron Trifluoride with Tetrahydropyran.—Boron trifluoride (15·4 mmoles) was passed slowly through tetrahydropyran (11·8 mmoles) at −40°; the liquid gradually became yellow. On warming to 20°, only 3·6 mmoles of boron trifluoride were recovered; hence equimolecular amounts (11·8 mmoles) had reacted, and no other material was formed. Molecular-weight determinations in nitrobenzene gave $M = 165$ ($C_5H_{10}O,BF_3$ requires M, 154), hence the 1 : 1 compound *tetrahydropyran–boron trifluoride*, m. p. ~ −18°, has been formed. The compound fumes in moist air, and finally leaves a residue of boric acid. Saturated vapour pressures were reproducible between 46° and 122°, and are represented by the equation $\log p + 2550/T = 8·74$; the molar latent heat (46—122°) is 11·7 kcal./mole and Trouton's constant is 26·8. The " boiling point," 162° at 760 mm. (by extrapolation), is not a true one, as tetrahydropyran–boron trifluoride is largely dissociated before the b. p. is reached. Vapour densities were measured over the range 83—118°, and the results are tabulated below. The calculated vapour density for the monomer $C_5H_{10}O,BF_3$ is 77; hence dissociation occurs above 83°, and to the extent of 91% at 118°. The heat of dissociation, based on a small number of readings, is 38 kcal.

Temp.	83°	94°	111·5°	118°
V.d., obs.	75·5	53	42·2	40·2

Reaction of Boron Trifluoride with Dioxan.—Boron trifluoride (15·1 mmoles) was passed through a 1 : 7 mixture of dioxan (14·1 mmoles) and light petroleum at 11°, until absorption of boron trifluoride ceased. A gelatinous mass formed and volatile products were removed at −30° and fractionated; only 0·51 mmole of boron trifluoride and unchanged light petroleum were recovered. The white solid residue in the reaction vessel was analysed [Found : BF_3, 43·4; B, 7·05; F, 36·2%; M, 321 (1·84% solution) 211 (3·86%). $C_4H_8O_2,BF_3$ requires BF_3, 43·6; B, 7·05; F, 36·6%; M, 156]. *Dioxan–boron trifluoride* fumes in moist air, and finally

leaves a residue of boric acid. Saturated vapour-pressure readings between 15° and 107° indicate slight irreversible secondary decomposition. The compound melts over the range 91—96°; the log p–$(1/T)$ plot is slightly curved, and indicates an apparent m. p. at 93°. A sample of the 1 : 1 compound, heated at 120° for 2½ hr. in a sealed tube, yielded only a trace of decomposition product on cooling; yet a sample heated in an open system at 50—60° yielded a colourless volatile liquid (v. p. 9 ± 2 mm. at 0°. Dioxan has v. p. 10 mm. at 0°) and a white solid (Found: BF_3, 58·9. $C_4H_8O_2,2BF_3$ requires BF_3, 60·7%).

Reaction of dioxan–boron trifluoride with water. A slight excess of water was condensed on to a sample of the 1 : 1 compound, and reaction allowed to proceed for several hours. Excess of water was removed at 60°, and the colourless crystals which separated, m. p. 140° (decomp.), were analysed (Found: F, 30·7. Calc. for $C_4H_8O_2,BF_3,2H_2O$: F, 29·7%); the dihydrate is reported to have m. p. 142° (decomp.) (Meerwein and Pannwitz, *loc. cit.*).

Reaction of dioxan–boron trifluoride with excess of boron trifluoride. Excess (142·4 mmoles) of boron trifluoride was condensed on dioxan–boron trifluoride (7·67 mmoles) at liquid-nitrogen temperature. The mixture was allowed to react at −112° for 6 hr., and unchanged boron trifluoride was removed at −112° and then at −78·5°. The reaction vessel was warmed to 20° and then re-cooled to −78·5°, until no more boron trifluoride was evolved; in all, 136·0 mmoles of boron trifluoride were recovered, so 6·4 mmoles react with 7·67 mmoles of dioxan–boron trifluoride. The white solid remaining in the reaction vessel was analysed [Found: BF_3, 59·7; F, 49·6%; *M*, 611 (1·83% solution), 272 (2·92%). $C_4H_8O_2,2BF_3$ requires BF_3, 60·7; F, 50·8%; *M*, 224]. For *dioxan–di(boron trifluoride)* saturated vapour-pressure readings are reproducible between 25° and 117°, and are represented by the equation $\log p + 2700/T = 9{\cdot}81$. The solid darkens slightly above 75°, but no m. p. is observed below 117°.

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Steroids. Part XI. Isolation of Cholegenin and* iso*Cholegenin from Ox-bile.*

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[Reprint Order No. 4881.]

The neutral fraction from ox-bile is shown to contain, in addition to much cholesterol, pregnane-3α : 20β-diol and two dihydric alcohols, $C_{27}H_{44}O_4$, named cholegenin and *iso*cholegenin. Cholegenin is converted into *iso*-cholegenin by the action of mineral acid.

It has frequently been reported that symptoms are considerably alleviated in patients suffering from rheumatoid arthritis if jaundice intervenes (for bibliography see Hench, Kendall, Slocumb, and Polley, *Assoc. Staff Meet., Mayo Clinic*, 1949, **24**, 181). This prompted us to examine the neutral fraction of ox-bile with the initial object of identifying the neutral steroid components. Apart from metabolic products intermediate between cholesterol and bile acids, there was reason to believe that bile contains pregnane derivatives which may be of value in a study of the relation between steroid metabolism and arthritis.

Pearlman (*J. Amer. Chem. Soc.*, 1944, **66**, 806) in an exploratory examination of the neutral, non-saponifiable fraction of ox-bile, isolated, in addition to cholesterol, five compounds, A—E, one of which, compound B, was identified later as *allo*pregnane-3β : 20β-diol (Pearlman, *J. Biol. Chem.*, 1946, **166**, 473): in a subsequent examination of ox-bile, he failed to isolate this pregnanediol. Pearlman and Cerceo later (*ibid.*, 1948, **176**, 847) isolated 3β-hydroxypregnan-20-one, pregnane-3α : 20β-diol, and *ætio*cholane-3α : 17β-diol from the neutral fraction from the bile of pregnant cows.

The procedure adopted by us for the isolation of the neutral fraction from ox-bile differs considerably from that used by Pearlman. After removal of the acids by treatment of the bile with cold barium hydroxide solution followed by digestion of the mass

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with chloroform, the neutral fraction was extracted with ether. The ether-soluble material was then extracted with light petroleum, and the insoluble fraction acetylated and chromatographed on alumina. In addition to a considerable amount of cholesteryl acetate, small quantities of the di- and mono-acetates of a compound, $C_{27}H_{44}O_4$, were isolated. This compound is a steroid sapogenin (see following paper) and, since it has been isolated from all samples of bile examined by us and is, we believe, an invariable constituent of ox-bile, we name it cholegenin. The mono- and di-acetates were interrelated by hydrolysis of each to cholegenin, and by further acetylation of the mono- to the di-acetate. Cholegenin and acetic anhydride in pyridine give the diacetate, which is partially hydrolysed on alumina to the monoacetate. The fraction soluble in light petroleum consisted essentially of cholesterol.

In an alternative method, the ether-soluble neutral fraction from bile was hydrolysed by alcoholic potassium hydroxide, and the non-saponifiable matter extracted with cold light petroleum which removed a fraction containing much cholesterol. The insoluble fraction was next extracted with boiling light petroleum, and the insoluble material chromatographed on alumina. Removal of a considerable amount of cholesterol from the fraction extracted with hot light petroleum was followed by chromatography of the residue on alumina. In this way, three homogeneous compounds were isolated, *viz.*, cholegenin, an isomer which we name *iso*cholegenin, and pregnane-3α : 20β-diol.

Pregnane-3α : 20β-diol was identified by direct comparison with a specimen prepared from progesterone,* hydrogenation of which over palladised charcoal yielded a mixture of pregnane- and *allo*pregnane-3 : 20-dione separated by trituration with methanol. Reduction of pregnane-3 : 20-dione with lithium aluminium hydride, followed by acetylation, yielded pregnane-3α : 20β-diol diacetate identical with the specimen isolated from bile. This identification was confirmed by a comparison of the corresponding diols. It is probable that Pearlman's compound D is pregnane-3α : 20β-diol; compound D was not obtained by Pearlman in sufficient quantity for analysis or for the determination of its specific rotation; the constants of its acetyl derivative (formulated as $C_{26}H_{42}O_4$ by Pearlman), m. p. 111°, $[\alpha]_D$ +72° (in EtOH), closely simulate those of pregnane-3α : 20β-diol diacetate {$C_{25}H_{40}O_4$, m. p. 113°, $[\alpha]_D$ +69° (in EtOH)}.

*iso*Cholegenin, $C_{27}H_{44}O_4$, is probably identical with Pearlman's compound C. Pearlman formulated compound C, which is not precipitated by digitonin, as $C_{25-26}H_{40-42}O_4$ and characterised it by the formation of a monoacetate under mild acetylation conditions. *iso*Cholegenin also is not precipitated by digitonin and on mild acetylation gives a monoacetate, with a smaller quantity of a diacetate. More drastic acetylation yields the diacetate; alkaline hydrolysis of the mono- or the di-acetate yields *iso*cholegenin. *iso*Cholegenin is probably formed from cholegenin during the isolation: it is obtained from the latter by the action of mineral acids. Cholegenin is the major component of the cholesterol-free neutral fraction from ox-bile, and Pearlman's failure to isolate it may well be due to its conversion into *iso*cholegenin (compound C) during the isolation procedure used by him.

Experimental

Specific rotations were measured in chloroform solution (unless otherwise stated) in a 1-dm. tube at approx. 15°. Grade II/III alumina, and a light petroleum fraction of b. p. 40—60° were used for chromatography.

Isolation of Cholegenin Diacetate and Cholegenin Monoacetate from Ox-bile.—Approx. 40 gallons of ox-bile were stirred with a solution of barium hydroxide [5 kg. $Ba(OH)_2,8H_2O$] in water (31 l.), and the mixture was extracted with chloroform (125 l.). The chloroform extract was filtered and the solvent evaporated under reduced pressure. The viscous dark green residue was dried in a vacuum over phosphoric oxide for 2 days, powdered, and extracted with ether (Soxhlet). Concentration of the extract gave a light brown powder (148 g., dried in a vacuum over P_2O_5). The powder was repeatedly extracted with boiling light petroleum (6 × 500 c.c.). The insoluble solid (10 g.) was separated; the combined, filtered extracts were

* The progesterone was given to us by Dr. C. L. Hewett, Organon Laboratories, Newhouse, Lanarkshire, to whom we express our best thanks.

concentrated, and the separating solid was collected and recrystallised from methanol, to yield cholesterol, m. p. and mixed m. p. 148—149°, $[\alpha]_D$ −40° (*c*, 3·5). Concentration of the light petroleum extracts gave additional amounts of cholesterol (total, 73 g.).

A sample (5 g.) of the solid insoluble in boiling light petroleum was kept with acetic anhydride (5 c.c.), pyridine (5 c.c.) and benzene (20 c.c.) at room temperature for 24 hr. and then heated under reflux for 2 hr. A solution of the acetylated product, isolated in the usual manner, in light petroleum was chromatographed on a column (27 × 2·5 cm.) of alumina. The column was washed with light petroleum (1550 c.c.) and then with light petroleum–benzene (19 : 1, 400 c.c.; 9 : 1, 600 c.c.; 4 : 1, 500 c.c.) which eluted a fraction (0·92 g.; m. p. 100—110°), recrystallisation of which from methanol yielded cholesteryl acetate as needles, m. p. and mixed m. p. 115—116°. Continued elution with light petroleum–benzene (1 : 1, 500 c.c.; 1 : 4, 450 c.c.) and benzene (300 c.c.) gave a fraction (0·59 g.; m. p. 140—170°), four crystallisations of which from ether–methanol gave *cholegenin diacetate* as fibrous needles, m. p. 174—175°, $[\alpha]_D$ −21°, −19° (*c*, 0·6, 0·7) (Found: C, 72·4, 72·25; H, 9·5, 9·65. $C_{31}H_{48}O_6$ requires C, 72·1; H, 9·4%). Continued elution with benzene (350 c.c.) and benzene–ether (4 : 1; 300 c.c.) gave a fraction (0·36 g.) which did not crystallise. A fourth fraction (0·98 g.; m. p. 130—180°) obtained by washing the column with benzene–ether (4 : 1, 600 c.c.; 1 : 1, 600 c.c.) and ether (500 c.c.) was crystallised four times from ether–light petroleum (b. p. 60—80°), to yield *cholegenin monoacetate* as needles, m. p. 192—193°, $[\alpha]_D$ −8°, −7° (*c*, 0·8) (Found: C, 73·5; H, 10·1. $C_{29}H_{46}O_5$ requires C, 73·4; H, 9·8%).

Cholegenin.—A solution of cholegenin diacetate (135 mg.) in methanolic potassium hydroxide (3%, 200 c.c.) was heated under reflux for 2 hr. The product was isolated by means of ether and crystallised from ether–light petroleum (b. p. 60—80°), to yield *cholegenin* as needles, m. p. 193°, $[\alpha]_D$ −27°, −25° (*c*, 0·8, 0·75) (Found: C, 75·2, 74·8; H, 10·4, 10·6. $C_{27}H_{44}O_4$ requires C, 74·95; H, 10·25%). Cholegenin does not give a colour with tetranitromethane in chloroform, does not show selective absorption between 2000 and 3500 Å, and does not give a precipitate with aqueous-alcoholic digitonin.

When cholegenin monoacetate (50 mg.) was similarly hydrolysed and the product crystallised from ether–light petroleum (b. p. 60—80°), it yielded cholegenin as needles, m. p. and mixed m. p. 193°, $[\alpha]_D$ −25° (*c*, 1·0).

Cholegenin (30 mg.) was kept in benzene (5 c.c.) with acetic anhydride (1 c.c.) and pyridine (1 c.c.) at room temperature for 24 hr. The product, isolated by means of ether and crystallised from ether–methanol, gave cholegenin diacetate as needles, m. p. and mixed m. p. 174—175°, $[\alpha]_D$ −19° (*c*, 0·6).

Cholegenin monoacetate (20 mg.) with pyridine (2 c.c.) and acetic anhydride (2 c.c.) at room temperature gave cholegenin diacetate, needles [from ether–light petroleum (b. p. 60—80°)], m. p. and mixed m. p. 173°.

Cholegenin diacetate (400 mg.) was adsorbed on alumina (10 g.) from a benzene solution, and the moist column kept for 7 days. Benzene (55 c.c.) then eluted a crystalline fraction (106 mg.; m. p. 170°) which after recrystallisation from ether–methanol gave the diacetate as needles, m. p. and mixed m. p. 173—174°. Continued washing of the column with benzene (125 c.c.) and benzene–ether (1 : 4; 50 c.c.) gave a fraction (55 mg.) which after recrystallisation from ether–light petroleum (b. p. 60—80°) gave cholegenin monoacetate as needles, m. p. and mixed m. p. 193°. A third fraction (20 mg.; m. p. 185—190°) was eluted with benzene–ether (1 : 1; 100 c.c.) and after recrystallisation from ether–light petroleum (b. p. 60—80°) gave cholegenin as needles, m. p. and mixed m. p. 193°.

Isolation of Cholegenin, Pregnane-3α : 20β-diol, and iso*Cholegenin.*—The dried solid (158 g.) obtained as described above from 40 gallons of ox-bile by treatment with barium hydroxide followed by extraction with chloroform was heated under reflux with ether for 24 hr. The ether-insoluble fraction (10 g.) was discarded. The solid obtained after removal of the solvent from the dried solution was heated under reflux with methanolic potassium hydroxide (5%; 3 l.). The non-saponifiable fraction (130 g.), isolated by means of ether, was heated under reflux for 15 min. with light petroleum (500 c.c., b. p. 60—80°), and the mixture cooled to room temperature and kept overnight. The insoluble solid (36 g.) was collected and heated under reflux with light petroleum (2 l.) for 36 hr. Filtration of the hot mixture gave a filtrate and a solid A (8·3 g.; see p. 1922). Removal of solvent from the filtrate gave a solid (27·7 g.) which readily crystallised from acetone, to yield cholesterol (21 g.), m. p. and mixed m. p. 148—149°. Crystallisation of the residue obtained by evaporation of the acetone mother-liquor, from methanol, gave more cholesterol (4·7 g.). Evaporation of the methanol mother-liquors provided an amorphous solid (1·98 g.), a solution of which in benzene (20 c.c.) was chromato-

graphed on alumina (50 g.). Benzene–ether (3 : 1, 600 c.c.) eluted a solid (903 mg.; m. p. 135—142°), crystallisation of which from methanol yielded cholesterol (750 mg.), m. p. and mixed m. p. 148—149°. Continued elution with benzene–ether (3 : 1, 300 c.c.) eluted a second fraction (236 mg.; m. p. 142—220°) which was triturated with a small volume of ether. The ether-soluble fraction crystallised from methanol, to yield cholesterol (149 mg.), m. p. and mixed m. p. 147°. A third fraction (243 mg.; m. p. 216—240°) obtained by washing the column with benzene–ether (3 : 1, 600 c.c.) was combined with the ether-insoluble part of the second fraction and, crystallised from ethyl acetate, gave needles (105 mg.), m. p. 218—219° (fraction 3*a*, see below.

Cholegenin. Continued washing of the column with benzene–ether (3 : 1, 150 c.c.; 1 : 1, 900 c.c.; 1 : 3, 450 c.c.) eluted a fourth fraction (314 mg.; m. p. 175—180°) which was thrice crystallised from ether–light petroleum (b. p. 60—80°), to yield cholegenin as needles, m. p. and mixed m. p. 193°, $[\alpha]_D$ −25° (*c*, 0·9).

Pregnane-3α : 20β-diol diacetate. (*a*) Fraction 3*a* was acetylated with pyridine and acetic anhydride, and the product was isolated by means of ether. A solution of this in light petroleum (10 c.c.) was filtered through neutral alumina (18 g.). A fraction (21 mg.; gum) eluted by light petroleum (175 c.c.) and light petroleum–benzene (3 : 1, 75 c.c.; 1 : 1, 75 c.c.) was not examined. Continued elution with light petroleum–benzene (1 : 1; 75 c.c.) gave a fraction (26 mg.; m. p. 110—111°) which on crystallisation from methanol followed by sublimation in a vacuum at 70—80° yielded pregnane-3α : 20β-diol diacetate (20 mg.) as needles, m. p. 113°, $[\alpha]_D$ +66° (*c*, 0·8) (Found: C, 74·1; H, 9·9. Calc. for $C_{25}H_{40}O_4$: C, 74·2; H, 10·0%).

(*b*) Hydrogenation of progesterone (1 g.) in ethanol (100 c.c.) in presence of palladised charcoal (10%; 80 mg.) (cf. Butenandt and Fleischer, *Ber.*, 1935, **68**, 2094) and trituration of the product with methanol (50 c.c.) gave *allo*pregnane-3 : 20-dione (insoluble); material recovered from the filtrate, when crystallised thrice from ether–light petroleum (b. p. 60—80°), yielded crude pregnane-3 : 20-dione as needles, m. p. 115°. A solution of the diketone in tetrahydrofuran (50 c.c.) was heated with lithium aluminium hydride (0·15 g.) under reflux for 30 min. The product, isolated in the usual manner, was triturated with cold ether (20 c.c.), and the insoluble fraction twice crystallised from chloroform–ethyl acetate, to yield pregnane-3α : 20β-diol, needles, m. p. 236°. Acetylation of the diol (210 mg.) with pyridine and acetic anhydride gave the diacetate, needles (from methanol), m. p. 113°, $[\alpha]_D$ +65°, +69° (*c*, 1·3, 1·2 in EtOH) (cf. Sarett, *J. Amer. Chem. Soc.*, 1949, **71**, 1179; Pearlman and Cerceo, *loc. cit.*; Meystre and Miescher, *Helv. Chim. Acta*, 1946, **29**, 33). A mixture with the specimen described under (*a*) had m. p. 113°.

Hydrolysis of pregnane-3α : 20β-diol diacetate (15 mg.) from ox-bile for 2 hr. with hot 3% methanolic potassium hydroxide (50 c.c.), followed by crystallisation (twice) from chloroform–ethyl acetate, yielded pregnane-3α : 20β-diol as fine needles, m. p. 235—236°, undepressed in m. p. when mixed with the specimen prepared from progesterone. Pearlman (1944, *loc. cit.*) gives m. p. 232—233° for compound D.

iso*Cholegenin.* (*a*) After removal of pregnane-3α : 20β-diol diacetate from the fraction 3*a* chromatogram, continued washing of the column with light petroleum–benzene (1 : 1; 225 c.c.) eluted a gum (3 mg.), whereafter benzene (75 c.c.) eluted a fraction (8 mg.; m. p. 226—228°) crystallisation of which from ether–methanol yielded iso*cholegenin diacetate* as long needles, m. p. 232—233°, $[\alpha]_D$ −38° (*c*, 0·8) (Found: C, 71·9; H, 9·6. $C_{31}H_{48}O_6$ requires C, 72·1; H, 9·4%). A final fraction (50 mg.; m. p. 183—184°) was obtained from the chromatogram by continued washing with benzene (300 c.c.) and then with benzene–ether (9 : 1; 150 c.c.). Four crystallisations of this from ether–light petroleum (b. p. 60—80°) yielded iso*cholegenin monoacetate* (10 mg.) as prisms, m. p. 187°, $[\alpha]_D$ −42° (*c*, 0·9) (Found: C, 72·9; H, 10·1. $C_{29}H_{46}O_5$ requires C, 73·4; H, 9·8%). Pearlman (1944, *loc. cit.*) gives m. p. 187° for the acetate of compound C.

A solution of *iso*cholegenin monoacetate (10 mg.) in 3% methanolic potassium hydroxide (50 c.c.) was heated under reflux for 2 hr. *iso*Cholegenin, isolated by means of ether, separated from ethyl acetate as needles which, after sublimation in a high vacuum at 200°, had m. p. 256—257° (decomp.), $[\alpha]_D$ −65°, −67° (*c*, 0·5, 0·6) (Found: C, 75·0, 74·8; H, 10·5, 10·6. $C_{27}H_{44}O_4$ requires C, 74·95; H, 10·25%). Pearlman (1944, *loc. cit.*) gives m. p. 260° for compound C. *iso*Cholegenin does not give a colour with tetranitromethane in chloroform, does not show selective absorption between 2000 and 3500 Å, and does not give a precipitate with aqueous-alcoholic digitonin.

*iso*Cholegenin (181 mg.) was acetylated with pyridine and acetic anhydride at room temperature, then chromatographed in light petroleum (10 c.c.) on alumina (8 g.). Light petroleum–benzene (3 : 2; 150 c.c.) eluted a solid (20 mg.; m. p. 217—230°), crystallisation of

which from ether–methanol gave *iso*cholegenin diacetate (9 mg.) as needles, m. p. and mixed m. p. 232—233°. Continued washing of the column with light petroleum–benzene (1 : 1; 200 c.c.) gave a fraction (55 mg.; m. p. 172—183°), which, after two crystallisations from ether–light petroleum (b. p. 60—80°), yielded *iso*cholegenin monoacetate as prisms, m. p. and mixed m. p. 187°.

*iso*Cholegenin (70 mg.) was refluxed with acetic anhydride (20 c.c.) for 14 hr. Recrystallisation of the product from ether–methanol yielded *iso*cholegenin diacetate as long needles (55 mg.), m. p. and mixed m. p. 232°.

(*b*) Cholegenin (200 mg.) in ethanol (50 c.c.) was refluxed with concentrated hydrochloric acid (10 c.c.) for 5 hr. The product was isolated by means of chloroform and crystallised several times from chloroform–ethyl acetate, to give *iso*cholegenin as fine needles, m. p. 252° (decomp.), $[\alpha]_D$ −67° (*c*, 0·8); a mixture with *iso*cholegenin described above was undepressed in m. p.

Dry hydrogen chloride was passed for 3 hr. through a solution of cholegenin (60 mg.) in chloroform (50 c.c.). After the mixture had been kept for 18 hr. at room temperature, the product was isolated by means of chloroform, to give a crystalline product, m. p. 214—220°, which after three recrystallisation from chloroform–ethyl acetate gave *iso*cholegenin as needles, m. p. and mixed m. p. 248—252°.

Examination of Solid A.—A solution of solid A (8·3 g.) in benzene (100 c.c.) was filtered through alumina (250 g.), and the column was washed with light petroleum–benzene (1 : 2, 200 c.c.), giving a crystalline fraction (6·0 g.; m. p. 144—147°), recrystallisation of which from methanol yielded cholesterol as plates, m. p. and mixed m. p. 147—148°. Continued washing with the same solvent mixture (500 c.c.) gave a second fraction, which was crystallised from chloroform–ethyl acetate, to give *iso*cholegenin as needles (181 mg.), m. p. and mixed m. p. 248—252° (decomp.).

The third fraction (1·3 g.; m. p. 170—180°) eluted with ether (375 c.c.) was acetylated by pyridine and acetic anhydride, the product being isolated by means of ether. A solution of this in light petroleum (50 c.c.) was filtered through neutral alumina (30 g.). The column was washed with light petroleum (675 c.c.), and with light petroleum–benzene (9 : 1, 300 c.c.; 4 : 1, 225 c.c.), to give a crystalline fraction (0·95 g.; m. p. 165—173°), recrystallisation of which from ether–methanol yielded cholegenin diacetate, m. p. and mixed m. p. 173—174°, $[\alpha]_D$ −23°, −21° (*c*, 1·1, 1·4). The column was then washed with light petroleum–benzene (4 : 1, 375 c.c.; 2 : 1, 75 c.c.; 1 : 1, 150 c.c.) which eluted a fraction (193 mg.; m. p. 138—168°). A third fraction (140 mg.; m. p. 183—190°) was obtained by elution with benzene (75 c.c.) and benzene–ether (9 : 1, 150 c.c.). Crystallisation of this fraction from ether–light petroleum (b. p. 60—80°) gave cholegenin monoacetate as needles, m. p. and mixed m. p. 192—193°, $[\alpha]_D$ −7° (*c*, 0·8).

The second fraction was hydrolysed for 2 hr. in hot ethanolic potassium hydroxide (3%; 50 c.c.). The product was isolated by means of ether (190 mg.), disssolved in benzene (20 c.c.), and filtered through alumina (8 g.). Benzene–ether (9 : 1, 525 c.c.; 1 : 1, 150 c.c.) and ether (150 c.c.) eluted a solid (180 mg.; m. p. 187—188°) which, after crystallisation from ether–light petroleum (b. p. 60—80°), gave cholegenin, m. p. and mixed m. p. 193°.

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Steroids. Part XII. The Structures of Cholegenin and* iso*Cholegenin.*

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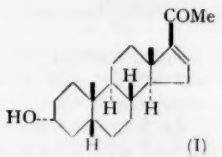
Cholegenin, obtained from ox-bile, is shown to be spirostane-3α : 27-diol (III); *iso*cholegenin differs from it in configuration at $C_{(25)}$.

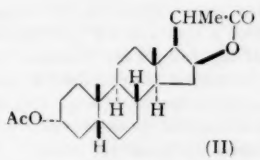
The preceding paper describes the isolation of cholegenin from ox-bile; a simplified method for this extraction is described in the Experimental section of this paper. Cholegenin, $C_{27}H_{44}O_4$, $[\alpha]_D$ −27°, forms a monoacetate and a diacetate; it is not unsaturated since it does not give a colour with tetranitromethane and does not show selective absorption between 2000 and 4000 Å. It does not contain a carbonyl group since it does not show low intensity selective absorption in the neighbourhood of 2800 Å or show carbonyl bands in the infra-red,† and it is not reduced by lithium aluminium hydride. Treatment of cholegenin with hydrochloric acid in ethanol or with hydrogen chloride in chloroform converts it into *iso*cholegenin without change in the function of the four oxygens. Cholegenin thus appears to contain two hydroxyl groups and two ether-like oxygen atoms. Its origin, lævorotation, molecular formula, and general properties all suggested that it may be a steroid sapogenin, and this view has been confirmed.

Treatment of *iso*cholegenin diacetate with acetic anhydride at 200—220° gives an oily product presumed to be a *pseudo*sapogenin acetate since in contrast to *iso*cholegenin diacetate it shows strong selective absorption at 2100 Å. Mild oxidation of the *pseudo*-sapogenin acetate with chromic acid followed by alkaline hydrolysis of the product gives a crystalline compound, $C_{21}H_{32}O_2$, which shows the characteristic ultra-violet absorption spectrum of an αβ-unsaturated ketone and was identified as 3α-hydroxypregn-16-en-20-one (I) (Marker, *J. Amer. Chem. Soc.*, 1940, **62**, 3350) by comparison with a specimen obtained by hydrolysis of a sample of its acetate kindly given to us by Dr. C. Djerassi of Wayne University, Detroit. A similar degradation of cholegenin also gave 3α-hydroxypregn-16-en-20-one.

Confirmation of the sapogenin-like nature of cholegenin was obtained by oxidation of its diacetate with chromic acid to an acetate-lactone, $C_{24}H_{36}O_4$, identified as 3α-acetoxy-16β-hydroxybisnorcholanic lactone (II) by comparison with a lactone obtained by similar oxidation of 3α-acetoxy*iso*spirostan (*epi*smilagenin acetate).



(I)



(II)

The conversion of cholegenin into 3α-hydroxypregn-16-en-20-one (I) and 3α-acetoxy-16β-hydroxybisnorcholanic lactone (II) shows that it is derived from spirostan-3α-ol by introduction of a second hydroxyl group into the fragment C_{23}—C_{27}. Evidence that the second hydroxyl group is primary and consequently attached to $C_{(27)}$ was adduced from the behaviour of cholegenin on oxidation with chromic acid. When mild reaction conditions are used the product is a keto-acid, $C_{27}H_{40}O_5$, characterised as its methyl ester. Reduction of the keto-acid with lithium aluminium hydride converted it into cholegenin. It follows that cholegenin is spirostane-3α : 27-diol (III).‡ Cholegenin and *iso*cholegenin differ in configuration at $C_{(25)}$. The latter is therefore termed, specifically, 25-*iso*cholegenin.

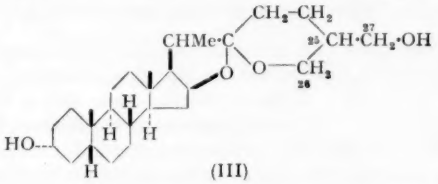
The infra-red absorption spectra of cholegenin and its derivatives have been examined

* Part XI, preceding paper.

† We are indebted to Professor E. R. H. Jones, F.R.S., and Dr. G. D. Meakins for this information.

‡ Configuration at $C_{(22)}$ is not implied by the designation or formula used for the spiro-ketal chain in (III).

in some detail by Professor H. H. Günthard, Zürich, to whom we express our best thanks for the following report. In addition to a strong band at 3410 cm.$^{-1}$ (hydroxyl) the spectrum of cholegenin shows a number of intense bands between 850 and 1300 cm.$^{-1}$ attributable to the spiro-ketal group; these include bands at 1009 and 1042 cm.$^{-1}$. Of the other bands, those at 920 and 900 cm.$^{-1}$ correspond to the ψ- and ω-bands of normal sapogenins (Jones, Katzenellenbogen, and Dobriner, *ibid.*, 1953, **75**, 158) both in location and in relative intensity, the former being more intense than the latter. The spectrum of



(III)

25-*iso*cholegenin on the other hand includes bands at 3290 cm.$^{-1}$ (hydroxyl) and a number of bands in the region 850—1300 cm.$^{-1}$, of which that at 923 cm.$^{-1}$ (T-band) is less intense than that at 895 cm.$^{-1}$ (U-band). In these respects cholegenin shows the characteristics of a normal sapogenin, and 25-*iso*cholegenin those of an *iso*sapogenin. A remarkable feature of the infra-red absorption spectrum of 25-*iso*cholegenin diacetate is worthy of comment. Although absorption bands at approximately 1730 and 1250 cm.$^{-1}$ attributable to the acetate group are present in the spectra of cholegenin diacetate and *iso*cholegenin monoacetate and diacetate, the last compound differs from the other two in that the 1250 cm.$^{-1}$ band is complex (peaks at 1222, 1250, 1253, and 1264 cm.$^{-1}$). This effect has been observed in a number of steroid acetates (Jones, Humphries, Herling, and Dobriner, *ibid.*, 1951, **73**, 3215; Fürst, Kuhn, Scotoni, and Günthard, *Helv. Chim. Acta*, 1952, **35**, 951) and, in all but one case, the acetoxy-group involved has the axial conformation, the corresponding epimeric (equatorial) acetate having an unresolved 1250-cm.$^{-1}$ band. Acetylation of 25-*iso*cholegenin with pyridine and acetic anhydride at room temperature yields mainly the monoacetate whereas similar treatment of cholegenin yields the diacetate. It is concluded that 25-*iso*cholegenin monoacetate is the 3-acetate and that the resolution of the 1250 cm.$^{-1}$ band of 25-*iso*cholegenin diacetate arises from a relatively hindered acetoxy group in the side chain.

Experimental

For general instructions see preceding paper. Ultra-violet absorption spectra were measured in ethanol with a Unicam S.P. 500 spectrophotometer.

Simplified Method for the Isolation of Cholegenin.—The neutral fraction (380 g.) from ox-bile (80 gallons), prepared as described in the preceding paper, was refluxed with ether (3 l.) for 24 hr. The ether-insoluble fraction (30 g.) was not examined. The ether-soluble fraction was boiled under reflux with ethanolic potassiumhydroxide (5%; 1·5 l.) for 3 hr. and the non-saponifiable fraction isolated by means of ether. This fraction was refluxed with light petroleum (2 l.) for 30 min., and set aside at room temperature overnight. The solid was collected and extracted with boiling light petroleum (500 c.c. × 5) and the insoluble residue A (32·6 g.) treated as described below. The combined hot light petroleum extracts were concentrated in vacuum, and the separating solid was collected and recrystallised from methanol, to yield cholesterol (49 g., m. p. and mixed m. p. (148—149°). Concentration of the methanol mother-liquor gave more cholesterol (5 g.), evaporation of the mother-liquor from which gave a residue B (2·4 g.). The light petroleum mother-liquor was evaporated, the residue (40 g.) combined with residues A and B, and the mixture chromatographed in benzene (150 c.c.) on alumina (1500 g.). Benzene (2 l.) and benzene–ether (4 : 1, 2·5 l.; 1 : 1, 2 l.; 2 : 3, 2 l.; 1 : 4, 1·75 l.) eluted a gum (4·26 g.). Continued elution with benzene–ether (2 : 3, 0·75 l.; 1 : 9, 1·7 l.) eluted a resin (6·5 g.) which, after trituration with methanol, gave cholesterol (3 g.), m. p. and mixed m. p. 148—149°. The next fraction (24·3 g.), which was eluted with benzene–ether (1 : 9, 6 l.), also gave cholesterol (20 g.), m. p. and mixed m. p. 148—149° after crystallisation from methanol. Continued washing of the column with the same solvent mixture (3·5 l.) gave a fraction (6·6 g.; m. p. 125—154°) which was triturated with ether (100 c.c.), crystallisation of the ether-soluble fraction (4·25 g.) from methanol giving

cholesterol (m. p. and mixed m. p.). The ether-insoluble fraction was not examined. The column was next washed with benzene–ether (1 : 9; 4 l.), ether (22·25 l.), and ether–methanol (99 : 1; 1 l.), to give a fraction (11·3 g.), m. p. 172—195°, which was triturated with cold ether (2 × 100 c.c.). The ether-soluble fraction was recrystallised (5 times) from ether–light petroleum (b. p. 60—80°), to yield cholegenin (4·1 g.) as needles, m. p. and mixed m. p. 192°, $[\alpha]_D$ −27° (*c*, 1·6). From the mother-liquors a further quantity of impure cholegenin (1·1 g.) was obtained, m. p. and mixed m. p. 185—187°. The fraction insoluble in ether, when crystallised four times from chloroform–ethyl acetate, gave *iso*cholegenin (0·3 g.) as fine needles, m. p. 249—254°, $[\alpha]_D$ −65° (*c*, 0·5); the m. p. of a mixture with an authentic specimen of m. p. 256° was undepressed.

3α-*Hydroxypregn*-16-*en*-20-*one from* 25-iso*Cholegenin*.—25-*iso*Cholegenin diacetate (200 mg.) in acetic anhydride was heated in a sealed tube at 200° for 10 hr. The oily product, isolated by means of ether, was chromatographed in light petroleum (5 c.c.) on neutral alumina (8 g.) prepared as described by Mancera, Barton, Rosenkranz, and Djerassi (*J.*, 1952, 1021). A fraction (oil; 45 mg.) eluted with light petroleum (150 c.c.) showed intense ultra-violet absorption with a maximum at 2100 Å (ε 7000). This was dissolved in acetic acid (80%; 10 c.c.) and treated dropwise during 10 min. at 15° with chromic acid (45 mg.) in acetic acid (2 c.c.; 80%). After 2 hr. at room temperature, the solution was treated with methanol; the neutral product was isolated by means of ether and refluxed for 35 min. with a solution of potassium hydrogen carbonate (2·4 g.) in methanol (70%; 50 c.c.). The hydrolysed neutral product (39 mg.) in light petroleum–benzene (1 : 1, 5 c.c.) was filtered through alumina (8 g.). Benzene–ether (50 : 1; 150 c.c.) eluted a solid which was sublimed in a high vacuum at 130°, crystallised from ether, and sublimed once more, to give 3α-hydroxypregn-16-en-20-one as prisms, m. p. 194—196°, $[\alpha]_D$ +57° (*c*, 0·5). Light absorption: Max. at 2390 Å (ε 8900) (Found: C, 79·7; H, 10·6. Calc. for $C_{21}H_{32}O_2$: C, 79·7; H, 10·2%).

An authentic sample of 3α-hydroxypregn-16-en-20-one was obtained by hydrolysis of its acetate (m. p. 103—106°) with aqueous potassium hydroxide in tetrahydrofuran. After chromatography on alumina, it separated from ether as prisms, m. p. 198—199°, $[\alpha]_D$ +60° (*c*, 0·9). Light absorption: Max. at 2390 Å (ε 9300). It was undepressed in m. p. when mixed with the specimen obtained from 25-*iso*cholegenin.

3α-*Hydroxypregn*-16-*en*-20-*one from Cholegenin*.—Cholegenin (0·46 g.) in acetic anhydride (10 c.c.) was kept at 220° for 16 hr. (sealed tube). The anhydride was decomposed with water, and the amorphous product isolated by means of ether. A solution of the product in acetic acid (80%; 10 c.c.) was treated dropwise during 10 min., with stirring, with chromic acid (0·4 g.) in acetic acid (80%; 5 c.c.) at 10—15°. After 2 hr. at room temperature the solution was treated with methanol. The neutral oxidation product (0·21 g.) was refluxed for 2 hr. with methanolic potassium hydroxide (3%; 50 c.c.), to give neutral (128 mg.) and acidic (86 mg.) fractions. A solution of the former in light petroleum–benzene (9 : 1; 10 c.c.) was filtered through alumina (8 g.). Benzene–ether (20 : 1, 150 c.c.) eluted a crystalline fraction which, after recrystallisation from ether and sublimation in a high vacuum at 120° (bath-temp.), gave 3α-hydroxypregn-16-en-20-one as prisms (from ether), m. p. 194—196°. Light absorption: Max. at 2390 Å (ε 8800). Mixtures with the specimens described above were undepressed in m. p.

Acetate-lactone $C_{24}H_{36}O_4$.—(*a*) The acidic fraction obtained by oxidation of cholegenin as described above was refluxed for 3 hr. with acetic acid (50 c.c.) containing hydrochloric acid (15%; 5 c.c.). The product was isolated by means of ether, and the neutral fraction (70 mg.) acetylated with acetic anhydride and pyridine at room temperature. The acetylated product in light petroleum (5 c.c.) was chromatographed on alumina (8 g.). Light petroleum–benzene (1 : 1; 150 c.c.) eluted a crystalline solid (35 mg.) which after two recrystallisations from ether–light petroleum gave the *acetate-lactone* as needles, m. p. 158°, $[\alpha]_D$ +3° (*c*, 0·4) (Found: C, 74·0; H, 9·6. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%).

(*b*) Cholegenin diacetate (350 mg.) in acetic acid (25 c.c.) was treated dropwise, with stirring, with chromic acid (380 mg.) in acetic acid (25 c.c.; 90%) at 80—90°. The mixture was kept at 90° for 1 hr., then treated with methanol, and the neutral product (53 mg.) was isolated with ether, and chromatographed in light petroleum (10 c.c.) on alumina (8 g.). The fraction eluted with light petroleum–benzene (2 : 1, 150 c.c.; 1 : 1, 150 c.c.) was twice recrystallised from ether–light petroleum (60—80°) and sublimed in a high vacuum at 140°, to give the lactone (15 mg.) as needles, m. p. 156—157°, $[\alpha]_D$ +2° (*c*, 0·9), undepressed in m. p. when mixed with the specimen described in (*a*).

(*c*) *epi*Smilagenin acetate (1 g.) (Djerassi, Yashin, and Rosenkranz, *J. Amer. Chem. Soc.*,

1952, **74**, 422) in acetic acid (40 c.c.) was treated dropwise during 45 min., with stirring, with chromic acid (1·2 g.) in acetic acid (80%; 10 c.c.) at 85—95° and the reaction mixture kept for 2 hr. at the same temperature. The neutral product (207 mg.) was recrystallised thrice from ether–light petroleum (b. p. 60—80°), to give the lactone, m. p. and mixed m. p. 157—159°, $[\alpha]_D$ −2° (*c*, 0·5) (Found: C, 74·1; H, 9·5%). The identity of the two specimens prepared by methods (*b*) and (*c*) was confirmed by a comparison of their infra-red absorption spectra kindly made by Professor H. H. Günthard. These were identical and each specimen showed bands (in Nujol) at 1770 (γ-lactone), 1721 and 1253 cm.$^{-1}$ (acetate).

Chromic Acid Oxidation of Cholegenin.—Cholegenin (500 mg.) in acetic acid was treated dropwise with chromic acid (550 mg.) in acetic acid (80%, 20 c.c.) with constant stirring at room temperature. After 4 hr. at room temperature, the excess of chromic acid was decomposed with methanol, and the product isolated by means of ether and separated into neutral (200 mg.) and acidic (300 mg.) fractions. The acidic fraction was recrystallised four times from aqueous acetone, to yield the *acid* (250 mg.) as plates, m. p. 197—201°, $[\alpha]_D$ −36° (*c*, 0·5) (Found: C, 72·2, 72·2; H, 9·0, 9·2. $C_{27}H_{40}O_5$ requires C, 72·9; H, 9·1. $C_{27}H_{40}O_5,\frac{1}{2}H_2O$ requires C, 72·1; H, 9·1%). The acid (200 mg.) was treated with ethereal diazomethane, and the neutral product thrice crystallised from light petroleum (b. p. 60—80°), to give the *methyl ester* as needles, m. p. 156°, $[\alpha]_D$ −67° (*c*, 0·8) (Found: C, 73·0; H, 9·5. $C_{28}H_{42}O_5$ requires C, 73·3; H, 9·2%). 2 : 4-Dinitrophenylhydrazine yields a crystalline precipitate.

Reduction of the Acid, $C_{27}H_{40}O_5$, with Lithium Aluminium Hydride.—The acid (30 mg.) in ether (40 c.c.) was refluxed with lithium aluminium hydride (100 mg.) for 30 min. After addition of ice and dilute acetic acid, the product was isolated with ether. A solution of the product in benzene was chromatographed on alumina (8 g.). The solid (24 mg.) eluted with benzene–ether (2 : 1, 150 c.c.; 1 : 1, 225 c.c.) and ether (75 c.c.) was recrystallised twice from ether–light petroleum (b. p. 60—80°), to yield cholegenin as needles, m. p. and mixed m. p. 191—192°, $[\alpha]_D$ −26° (*c*, 0·6).

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Steroids. Part LII. Synthesis of Steroidal Hormone Analogues Hydroxylated at $C_{(6)}$.*

By (MISS) C. AMENDOLLA, G. ROSENKRANZ, and FRANZ SONDHEIMER.

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Oxidation of 3β : 6β-dihydroxy-Δ^4-steroids (generally obtainable from the 3β-hydroxy-Δ^5-steroids by a simple and efficient four-step sequence) by manganese dioxide in chloroform at room temperature is shown to provide a general synthesis of 6β-hydroxy-3-keto-Δ^4-steroids. The reaction is employed for the synthesis of 6β-hydroxycholest-4-en-3-one (VI*a*), 6β-hydroxyprogesterone (VI*b*), 6β-hydroxydeoxycorticosterone 21-acetate (VI*c*), 6β-hydroxyandrost-4-ene-3 : 17-dione (VI*d*), 6β-hydroxytestosterone (VI*e*), and 6β : 17α-dihydroxyprogesterone (VI*f*). At the boiling point the 3 : 6-diketo-Δ^4-compounds are formed.

IN view of the physiological action of the 11β-hydroxylated hormone, 11β : 17α : 21-trihydroxypregn-4-ene-3 : 20-dione (Kendall's compound F), it is of interest to investigate the activity of steroidal hormone analogues with hydroxyl groups in positions other than at $C_{(11)}$, and for this reason we undertook the preparation of Δ^4-3-ketones hydroxylated at $C_{(6)}$. Moreover such compounds are produced from the Δ^4-3-ketones by microbiological

* Part LI, Sondheimer, Amendolla, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 5932. A preliminary announcement has been made of part of the present work (Sondheimer and Rosenkranz, *Experientia*, 1953, **9**, 62).

methods (Peterson, Murray, *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 5933; 1953, **75**, 408, 412, 416; Abs. Papers, 123rd Meeting Amer. Chem. Soc., 1953, p. 5c), and by incubation with adrenal breis (Haines, " Recent Progress in Hormone Research," Academic Press, New York, 1952, **7**, 282) or with *corpus luteum* homogenates (Berliner, Mont, and Zaffaroni, *J. Amer. Chem. Soc.*, in the press). The latter observations especially are of interest, since they indicate that the 6-hydroxy-Δ^4-3-ketones may well play a significant role in human physiology.

The only chemical method of general applicability hitherto described for preparing 6-hydroxy-Δ^4-3-ketones involves the conversion of a 3β-hydroxy-Δ^5-steroid into the 6β-acetoxy-3β : 5α-dihydroxy-compound by any of several methods, followed by oxidation at $C_{(3)}$ and dehydration at positions 4 : 5 (*inter al.*, Ellis and Petrow, *J.*, 1939, 1078; Ehrenstein *et al.*, *J. Org. Chem.*, 1940, **5**, 318; 1941, **6**, 626, 908; 1951, **16**, 1050; 1952, **17**, 1587; cf. Dane, Wang, and Schulte, *Z. physiol. Chem.*, 1936, **245**, 80). Moreover Professor L. F. Fieser has informed us that 6β-hydroxycholest-4-en-3-one is obtained directly in 16·5% yield from cholesterol by oxidation with sodium dichromate (*J. Amer. Chem. Soc.*, 1953, **75**, 4377).

We now report a new general synthesis of 6β-hydroxy-3-keto-Δ^4-steroids, by partial oxidation of the 3β : 6β-dihydroxy-compounds by manganese dioxide at room temperature (V ⟶ VI). We have applied this method in six cases (*a*—*f*; see reaction scheme).

Use of this oxidant in boiling chloroform gives the Δ^4-3 : 6-diones (examples investigated were VII*a*, *b*, *c*, *d*, and *e*). It is noteworthy that both the 6- and the 3-hydroxyl group are oxidised even at room temperature when the former hydroxyl group is equatorial as in cholest-4-ene-3β : 6α-diol.

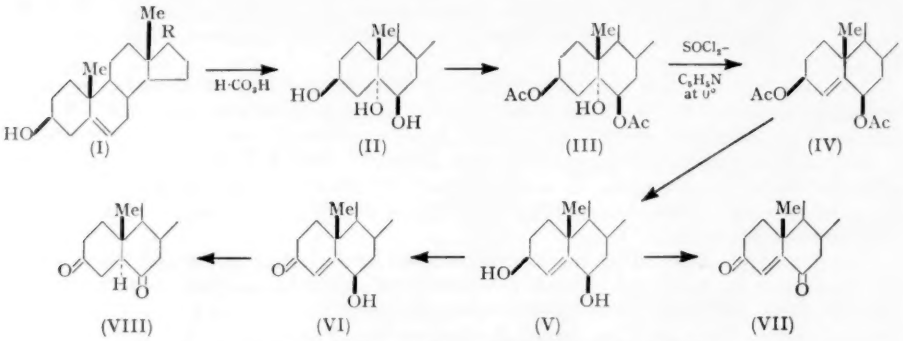
Further applications of the method follow from isomerisation of the acetates of (VI) to the 6α-isomers by hydrogen chloride in chloroform containing alcohol (Ehrenstein *et al.*, *locc. cit.*, 1951, 1952), and from alkaline isomerisation of (VI) to (VIII) (examples reported are *b*, *d*, and *e*; these reactions served as confirmation of structure). It is of interest that lithium in liquid ammonia removes the 6β-hydroxyl group from (VI) to give the 3-keto-Δ^4-steroids (6β-hydroxytestosterone ⟶ testosterone), and the same products are obtained by treating the 6β-acetoxy-compounds with zinc and acetic acid (6β-acetoxyprogesterone ⟶ progesterone). Professor L. F. Fieser (*loc. cit.*)has in dependently reported the latter type of reaction.

The nature of the product (VI) was first proved for 6β-hydroxycholest-4-en-3-one (VI*a*). This and its acetate were identical with known materials (Ellis and Petrow, *loc. cit.*; Romo, Rosenkranz, Djerassi, and Sondheimer, *J. Org. Chem.*, in the press) and different from those of the other possible keto-alcohol (3β-hydroxycholest-4-en-6-one) and its acetate (Heilbron, Jones, and Spring, *J.*, 1937, 801). The products (VI*b*—*f*) were identified by their similarity or that of their acetates or of the derived diketones (VII or VIII) (see above) to recorded compounds (see Experimental section for details). The 6-acetoxyprogesterone (cf. VI*b*) prepared by Ehrenstein *et al.* (*loc. cit.*, 1940) is shown to be the 6β-compound, and this is in line with later work of that school (*loc. cit.*, 1952). On the other hand it is concluded that the 6-acetoxyandrost-4-ene-3 : 17-dione of Ehrenstein (*J. Org. Chem.*, 1941, **6**, 626) must have the 6α-configuration, since it differs from the 6β-acetoxy-compound (VI*d*) prepared by the manganese dioxide route, and this again is in agreement with the recent publication of Ehrenstein *et al.* (*loc. cit.*, 1952).

The 3β : 6β-dihydroxy-Δ^4-steroids (V) used in these syntheses are readily obtained from the accessible 3β-hydroxy-Δ^5-compounds by the reaction sequence (I) ⟶ (II) ⟶ (III) ⟶ (IV) ⟶ (V). In the cholesterol series (*a*) all these reactions are so smooth (cf. Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1949, **71**, 3938; Petrow, Rosenheim, and Starling, *J.*, 1938, 677) that the overall yield of the final product (VI*a*) from cholesterol (I*a*) is *ca.* 60%. Of the materials used in this work, (V*a*), (V*b*), and (IV*c*) were known, and the conversion of the last-named substance into (V*c*) by hydrolysis and partial acetylation at $C_{(21)}$ offered no difficulty. In the androstan-17-one series (*d*), Davies and Petrow (*J.*, 1949, 2536) reported that the dehydration step, (III*d*) ⟶ (IV*d*), occurred only under reflux, and then slowly and in only *ca.* 50% yield. However in our hands an 80% yield was readily obtained under the usual conditions (0°), and hydrolysis then led smoothly to the required (V*d*). Androst-4-

ene-3β : 6β : 17β-triol (V*e*) was simply prepared by reduction of the 17-keto-3β : 6β-diacetate (IV*d*) with lithium aluminum hydride. 6β : 17α-Dihydroxyprogesterone (VI*f*) has been obtained microbiologically from 17α-hydroxyprogesterone (Peterson, Murray, *et al.*, *loc. cit.*, p. 416) but its chemical preparation required variation of our standard procedure : performic oxidations of 3β : 17α-dihydroxy- (I*f*) and 3β-acetoxy-17α-hydroxy-pregn-5-en-20-one did not proceed well owing to unfavourable solubilities, but the more soluble 3β : 17α-diacetate reacted normally ; hydrolysis with potassium carbonate then gave the 3β : 5α : 6β-trihydroxy-17α-acetate (II*g*) which was converted normally into (III*g*) and (IV*g*), whence hydrolysis removed the last acetyl group, to give the required (V*f*).

Recent papers by Ehrenstein and by Peterson, Murray, and their collaborators (*locc. cit.*), as well as the present work, show that introduction of a 6β-hydroxy- or a 6β-acetoxy-group into 3-keto-Δ^4-steroids lowers the position of maximum ultra-violet absorption by *ca.*



a, R = $-C_8H_{17}$. *b*, R = –COMe. *c*, R = $-CO\cdot CH_2\cdot OAc$. *d*, R = :O.
e, R = –OH. *f*, R = . *g*, R = .

40 Å (to *ca.* 2360 Å) and the intensity (ε) by about 2000 (to 12,500—14,000). On the other hand the 3β-hydroxy-Δ^4-6-ketone in the cholestane series exhibits a maximum with a markedly more reduced intensity ($\lambda_{max.}$ 2390 Å; ε 6300) (Heilbron, Jones, and Spring, *loc. cit.*), doubtless owing to the *s-cis* configuration of the αβ-unsaturated ketone system in this case (Turner and Voitle, *J. Amer. Chem. Soc.*, 1951, **73**, 1403). A compound prepared by Davis and Petrow (*loc. cit.*) from 3β : 6β-dihydroxyandrost-4-en-17-one (V*d*) by chromic acid oxidation has an absorption maximum of such high intensity (ε 13,000 at 2370 Å) that it is clearly the 6β-hydroxy-3-ketone (VI*d*). This contradicts the earlier assignment to it of the 3β-hydroxy-6-ketone structure, which followed from a confusion about the stereochemistry at $C_{(6)}$ of 6-acetoxyandrost-4-ene-3 : 17-dione, but is confirmed by agreement of the properties recorded by Davis and Petrow for their compound and its acetate with those of (VI*d*) and its acetate prepared by us.

A number of compounds described in this paper are being tested for their biological properties, and the results will be published subsequently.

Experimental

Rotations were measured in $CHCl_3$ and ultra-violet absorption spectra in 95% EtOH solution unless specified otherwise. Infra-red spectra were obtained, with $CHCl_3$ solutions (unless otherwise stated) and a Perkin-Elmer 12C single-beam spectrophotometer with a sodium chloride prism. We are indebted to Miss Paquita Revaque for these measurments and to Miss Amparo Barba for the microanalyses. The manganese dioxide was prepared from potassium permanganate and manganese sulphate, as described by Mancera, Rosenkranz, and Sondheimer (*J.*, 1953, 2189).

6β-*Hydroxycholest-4-en-3-one* (VI*a*).—A suspension of the 4-ene-3β : 6β-diol (V*a*) (10 g.; finely ground) (Petrow, Rosenheim, and Starling, *J.*, 1938, 677) in chloroform (1 l.) was shaken

with manganese dioxide (100 g.) at room temperature for 24 hr. The dioxide was removed by filtration and washed well with hot chloroform. Crystallization of the product from chloroform–acetone furnished the unsaturated hydroxy-ketone (VI*a*) (6·9 g.), m. p. 188—192°, $\lambda_{max.}$ 2360 Å (ε 13,300). One further crystallization gave material with constant m. p. 194—195°, $[\alpha]_D^{20}$ +38° in dioxan, $\nu_{max.}$ 1670 cm.$^{-1}$ (unsaturated ketone) and a free-hydroxyl band (Ellis and Petrow, *loc. cit.*, give m. p. 192°). Chromatographic purification on alumina of the mother-liquors after removal of the 6·9 g. of (VI*a*) furnished another 0·4 g. of this product, m. p. 190—193° (total yield, 73%), and the 3 : 6-dione (VII*a*) (0·3 g.), m. p. 118—121°. Similar results were obtained when the reaction was performed in benzene suspension.

The 6-acetate was prepared with acetic anhydride and pyridine (steam-bath, 1 hr.) and crystallized from methanol as needles, m. p. 103—104°, $[\alpha]_D^{20}$ + 40° in dioxan, $\lambda_{max.}$ 2360 Å (ε 12,800), $\nu_{max.}$ 1736 (acetate) and 1672 cm.$^{-1}$ (unsaturated ketone) (Ellis and Petrow, *loc. cit.*, give m. p. 101·5°, $[\alpha]_D^{19}$ +36°).

Cholest-4-ene-3 : *6-dione* (VII*a*).—(*a*) A stirred solution of cholest-4-ene-3β : 6β-diol (V*a*) (1 g.) in chloroform (600 c.c.) was heated under reflux with manganese dioxide (20 g.) for 6 hr. The total crude product ($\lambda_{max.}$ 2500 Å; ε 9200) was chromatographed on alumina (50 g.). Combination of the fractions eluted with hexane–benzene (1 : 2) and crystallization from methanol furnished the diketone (0·46 g.), m. p. 122—124°, $[\alpha]_D^{20}$ −36°, $\lambda_{max.}$ 2500 Å (ε 11,200), $\nu_{max.}$ 1688 cm.$^{-1}$ (Δ^4-3 : 6-dione; cf. Jones, Humphries, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 956) (*inter al.*, Ross, *J.*, 1946, 737, gives m. p. 124—125°, $[\alpha]_D^{20}$ −38°).

(*b*) [With J. Herrán.] A solution of cholest-4-ene-3β : 6α-diol (1 g.; Prelog and Tagmann, *Helv. Chim. Acta*, 1944, **27**, 1867) in benzene (100 c.c.) was shaken with manganese dioxide (10 g.) for 20 hr. at room temperature. Crystallization of the product from methanol yielded the 3 : 6-dione (0·68 g.), m. p. 123—125°, $\lambda_{max.}$ 2500 Å (ε 10,900), identified with the sample obtained above by a mixed m. p. determination and comparison of the infra-red spectra. The mother-liquors exhibited $\lambda_{max.}$ 2480 Å (ε 10,200) and therefore contained essentially the diketone.

3β : 6β-*Dihydroxypregn-4-en-20-one* (V*b*).—A solution of 3β : 6β-diacetoxypregn-4-en-20-one (IV*b*) (21 g.; Mancera, Rosenkranz, and Djerassi, *J. Org. Chem.*, 1951, **16**, 192) in methanol (1050 c.c.) was heated under reflux with sodium hydroxide (16 g.) in water (105 c.c.) for 1 hr. The solution was concentrated, then poured into water, and the product collected. Crystallization from methanol yielded the diol (V*b*) (12·5 g.), m. p. 193—196°. Further crystallization led to a specimen with m. p. 201—203°, $[\alpha]_D^{20}$ +95°, $\nu_{max.}$ 1700 cm.$^{-1}$ (saturated ketone) and a free-hydroxyl band (Found: C, 75·95; H, 9·45. Calc. for $C_{21}H_{32}O_3$: C, 75·85; H, 9·7%) (Davis and Petrow, *J.*, 1950, 1185, give m. p. 198—200°).

6β-*Hydroxyprogesterone* (VI*b*).—A suspension of 3β : 6β-dihydroxypregn-4-en-20-one (10 g.; finely ground) in chloroform (1 l.) was shaken with manganese dioxide (100 g.) at room temperature for 24 hr. The dioxide was removed by filtration and washed very thoroughly with hot chloroform. Crystallization of the product from acetone–ether yielded 6β-hydroxyprogesterone (6·3 g.), m. p. 173—175°. A purified sample exhibited m. p. 179—180°, $[\alpha]_D^{20}$ +105°, $\lambda_{max.}$ 2360 Å (ε 13,600), $\nu_{max.}$ 1700 (saturated ketone) and 1672 cm.$^{-1}$ (unsaturated ketone) and a free-hydroxyl band (Found: C, 76·0; H, 9·3. Calc. for $C_{21}H_{30}O_3$: C, 76·3; H, 9·15%) (Balant and Ehrenstein, *J. Org. Chem.*, 1952, **17**, 1587, give m. p. 178—179°, $[\alpha]_D^{28}$ +107°).

The 6-acetate, prepared as above, crystallized from ether–hexane. It exhibited m. p. 144—145°, $[\alpha]_D^{19}$ +92° in EtOH, $\lambda_{max.}$ 2360 Å (ε 13,200), $\nu_{max.}$ 1736 (acetate), 1700 (saturated ketone), and 1674 cm.$^{-1}$ (unsaturated ketone) (Ehrenstein and Stevens, *ibid.*, 1940, **5**, 318, give m. p. 145—146°, $[\alpha]_D^{18}$ +90° in EtOH; Balant and Ehrenstein, *loc. cit.*, give m. p. 147—148°, $[\alpha]_D^{22}$ +101°).

Reduction of 6β-*Acetoxyprogesterone to Progesterone* [*with* H. Martinez].—A mixture of zinc dust (1 g.) and 6β-acetoxyprogesterone (0·50 g.) in acetic acid (10 c.c.) and water (3 c.c.) was stirred at room temperature for 2 hr. The filtered solution was evaporated almost to dryness, diluted with water, and extracted with chloroform. The zinc residue was extracted with hot chloroform, and the combined chloroform solutions were washed with aqueous sodium hydrogen carbonate, dried, and evaporated. Crystallization of the residue from acetone–hexane furnished progesterone (0·22 g.), m. p. 127—130°, identified with an authentic specimen (m. p. 128—130°) by mixed m. p. determination and comparison of infra-red spectra.

allo*Pregnane-3* : *6* : *20-trione* (VIII*b*).—A solution of 6β-hydroxyprogesterone (0·2 g.) in methanol (10 c.c.) was heated under reflux under nitrogen with potassium hydroxide (0·2 g.) in water (1 c.c.) for 30 min. Crystallization of the product from acetone–ether yielded the triketone, m. p. 231—233°, $[\alpha]_D^{20}$ +65° in dioxan, no high-intensity absorption in the ultra-violet, $\nu_{max.}$ 1700 cm.$^{-1}$ (saturated ketone), no free-hydroxyl band (Moffett, Stafford, Linsk, and Hoehn,

J. Amer. Chem. Soc., 1946, **68**, 1857, give m. p. 227—230·5°, $[\alpha]_D^{23}$ +53° in dioxan; Balant and Ehrenstein, *loc. cit.*, give m. p. 232·5—233°, $[\alpha]_D^{28}$ +61°).

6-*Oxoprogesterone* (VII*b*).—3β : 6β-Dihydroxypregn-4-en-20-one (V*b*) (0·70 g.), manganese dioxide (7 g.), and chloroform (70 c.c.) were heated under reflux with stirring for 6 hr. The residue ($\lambda_{max.}$ 2500 Å, ε 8200) was chromatographed on alumina (35 g.), and the fractions eluted with hexane–benzene (2 : 1) were pooled. Crystallization from chloroform–ether furnished 6-oxoprogesterone (0·36 g.), m. p. 193—194°, $[\alpha]_D^{20}$ +30°, $\lambda_{max.}$ 2500 Å (ε 10,600), $\nu_{max.}$ 1700 (saturated ketone) and 1686 cm.$^{-1}$ (Δ^4-3 : 6-dione) (Found : C, 76·8; H, 8·85. Calc. for $C_{21}H_{28}O_3$: C, 76·8; H, 8·6%) (Ehrenstein, *J. Org. Chem.*, 1939, **4**, 506, gives m. p. 185—188°; Moffett, Stafford, Linsk, and Hoehn, *loc. cit.*, give m. p. 185—187°).

3β : 6β : 21-*Trihydroxypregn-4-en-20-one*.—An ice-cooled solution of sodium hydroxide (13 g.) in water (60 c.c.) was added to a solution of 3β : 6β : 21-triacetoxypregn-4-en-20-one (IV*c*) (13 g.) (Mancera, Rosenkranz, and Djerassi, *loc. cit.*) in ice-cold methanol (300 c.c.) in an atmosphere of nitrogen. After being allowed to reach room temperature, the solution was set aside under nitrogen overnight. The base was neutralized by excess acetic acid, and the solution was concentrated to small volume and then diluted with water. Extraction with chloroform and crystallization from methanol–ether furnished the *triol* (8·1 g., 85%), m. p. 200—203°. The analytical sample exhibited m. p. 204—206°, $[\alpha]_D^{20}$ +82°, $\nu_{max.}$ (mull) 1700 cm.$^{-1}$ (saturated ketone) and a free-hydroxyl band (Found : C, 72·1; H, 9·4. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·25%).

21-*Acetoxy*-3β : 6β-*dihydroxypregn-4-en-20-one* (V*c*).—A solution of the above triol (5·0 g.) in anhydrous pyridine (13 c.c.) was cooled to −10°, and acetic anhydride (1·76 g., 1·2 mols.) was added. After being kept overnight at −10°, the solution was diluted with water, and the product isolated in the usual way. Chromatographic purification and crystallization from acetone yielded the 21-*monoacetate* (2·6 g. of m. p. 190—192°), m. p. 195—196°, $\nu_{max.}$ 1744 and 1718 cm.$^{-1}$ (21-acetoxy-20-ketone; cf. Jones, Dobriner, *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 2024; 1950, **72**, 956) and a free-hydroxyl band (Found : C, 70·4; H, 8·5. $C_{23}H_{34}O_5$ requires C, 70·75; H, 8·8%). In later experiments a polymorphic form, m. p. 217—219°, was obtained.

6β-*Hydroxydeoxycorticosterone* 21-*Acetate* (VI*c*).—A solution of the triol monoacetate (V*c*) (4·5 g.) in chloroform (450 c.c.) was shaken with manganese dioxide (45 g.) at room temperature for 24 hr. Isolation in the usual manner and crystallization from acetone–hexane yielded 6β-hydroxydeoxycorticosterone 21-acetate (2·81 g. of m. p. 192—195°), m. p. 198—199°, $[\alpha]_D^{20}$ +105°, $\lambda_{max.}$ 2360 Å (ε 12,900), $\nu_{max.}$ 1744 and 1718 (21-acetoxy-20-ketone) and 1670 cm.$^{-1}$ (unsaturated ketone), and a free-hydroxyl band (Found : C, 71·4; H, 8·3. Calc. for $C_{23}H_{32}O_5$: C, 71·1; H, 8·3%) (Eppstein *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 408, give m. p. 196—198°, $[\alpha]_D^{23}$ +113°, for the product obtained by monoacetylation of the free diol, prepared by a microbiological method).

The 6 : 21-diacetate, prepared as above and crystallized from ether–pentane, had m. p. 130—131°, $[\alpha]_D^{20}$ +102°, $\lambda_{max.}$ 2360 Å (ε 13,100), $\nu_{max.}$ 1742 and 1718 (21-acetoxy-20-ketone and acetate), 1672 cm.$^{-1}$ (unsaturated ketone), and no free-hydroxyl band (Found : C, 69·45; H, 8·1. Calc. for $C_{25}H_{34}O_6$: C, 69·75; H, 7·95%) (Eppstein *et al.*, *loc. cit.*, give m. p. 127—129°, $[\alpha]_D^{23}$ +103°, for a microbiological product, and Herzig and Ehrenstein, *J. Org. Chem.*, 1951, **16**, 1050, give m. p. 125—127°, $[\alpha]_D^{16}$ +110°).

6-*Oxodeoxycorticosterone* 21-*Acetate* (VII*c*).—A solution of 3β : 6β-dihydroxy-21-acetoxypregn-4-en-20-one (V*c*) (1·0 g.) in chloroform (100 c.c.) was heated under reflux with manganese dioxide (10 g.) for 8 hr., with stirring. The product ($\lambda_{max.}$ 2480 Å, ε 8700) was chromatographed on alumina (50 g.), and the fractions eluted with benzene were pooled and crystallized from acetone–ether. The resulting 6-*oxodeoxycorticosterone acetate* (0·42 g.) showed m. p. 138—139°, $[\alpha]_D^{20}$ +36°, $\lambda_{max.}$ 2500 Å (ε 10,800), $\nu_{max.}$ 1744 and 1718 (21-acetoxy-20-ketone), 1688 cm.$^{-1}$ (Δ^4-3 : 6-dione), and no free-hydroxyl band (Found : C, 71·45; H, 7·95. $C_{22}H_{30}O_5$ requires C, 71·5; 7·8%).

3β : 6β-*Diacetoxy*-5α-*hydroxyandrostan*-17-*one* (III*d*).—3β-Hydroxyandrost-5-en-17-one (I*d*) (140 g.) was heated on the steam-bath with formic acid (840 c.c.; 90%) for 5 min., cooled to room temperature, and then treated with hydrogen peroxide (140 c.c.; 30%) in small portions, the temperature being kept below 40°. After 6 hr. at room temperature, water was added, and the precipitate was collected. This was then heated under reflux for 15 min. with potassium hydroxide (40 g.) in methanol (1·4 l.) and water (140 c.c.). Evaporation under reduced pressure, addition of water, and filtration yielded 3β : 5α : 6β-trihydroxyandrostan-17-one (II*d*) (73 g.), m. p. 297—300° (Zelinskii and Ushakov, *Bull. Acad. Sci., Russia*, 1936, 879, give m. p. 301—302°; Miescher and Fischer, *Helv. Chim. Acta*, 1938, **21**, 336, give m. p. 299—302°).

Acetylation of the above triol (35 g.) as usual and crystallization from ether–hexane afforded

the 3 : 6-diacetate (III*d*) (39·2 g. of m. p. 178—182°), m. p. 184—185°, $[\alpha]_D^{20}$ −3°, $\nu_{max.}$ 1732 cm.$^{-1}$ (acetate and 17-ketone) and a free-hydroxyl band (Found: C, 67·75; H, 8·25. Calc. for $C_{23}H_{34}O_6$: C, 67·95; H, 8·45%) (Zelinskii and Ushakov, *loc. cit.*, give m. p. 171—172°; Ehrenstein and Decker, *J. Org. Chem.*, 1940, **5**, 544; 1941, **6**, 626, give m. p. 216·5—217°).

The discrepancy in m. p. with that given by Ehrenstein and Decker was due to polymorphism. When recrystallized in the presence of a trace of material (m. p. 215—216°) kindly supplied by Dr. Ehrenstein, the m. p. rose directly to 216—218°, and there was no m. p. depression on admixture with Dr. Ehrenstein's sample.

3β : 6β-*Diacetoxyandros*-4-*en*-17-*one* (IV*d*) (cf. Davis and Petrow, *J.*, 1949, 2536).—Thionyl chloride (10·5 c.c.) was added to an ice-cooled solution of 5α-hydroxy-3β : 6β-diacetoxyandrostan-17-one (35 g.) in pyridine (160 c.c.). After 5 min. at 0°, the product was precipitated with water and crystallized from acetone–hexane. In this way the unsaturated diacetate (26·5 g., 80%), m. p. 156—160°, was obtained. Further crystallization yielded material with m. p. 163—164°, $\nu_{max.}$ 1736 cm.$^{-1}$ (acetate and 17-ketone) and no free-hydroxyl band (Found: C, 71·0; H, 8·4. Calc. for $C_{23}H_{32}O_5$: C, 71·1; H, 8·3%) (Davis and Petrow, *loc. cit.*, give m. p. 163—164°).

3β : 6β-*Dihydroxyandrost*-4-*en*-17-*one* (V*d*).—This substance was obtained in *ca.* 75% yield by heating the preceding diacetate with sodium hydroxide in methanol for 1 hr. Crystallized from acetone–methanol, it had m. p. 274—276°, $\nu_{max.}$ (mull) 1736 cm.$^{-1}$ (17-ketone) and a free-hydroxyl band (Davis and Petrow, *loc. cit.*, give m. p. 269—270°).

6β-*Hydroxyandrost*-4-*ene*-3 : 17-*dione* (VI*d*).—A suspension of 3β : 6β-dihydroxyandrost-4-en-17-one (V*d*) (2·5 g.; finely ground) in chloroform (250 c.c.) was shaken at room temperature with manganese dioxide (25 g.) for 24 hr. Crystallization from methanol–ether afforded 6β-hydroxyandrost-4-ene-3 : 17-dione (1·67 g. of m. p. 186—190°), m. p. 192—193°, $[\alpha]_D^{20}$ +114°, $\lambda_{max.}$ 2360 Å (ε 13,200), $\nu_{max.}$ 1736 (17-ketone), 1672 cm.$^{-1}$ (unsaturated ketone), and a free-hydroxyl band (Found: C, 75·2; H, 8·35. Calc. for $C_{19}H_{26}O_3$: C, 75·45; H, 8·65%). Davis and Petrow, *loc. cit.*, give m. p. 192—193° for this substance, then believed to be the 3-hydroxy-Δ^4-6-ketone; Balant and Ehrenstein, *loc. cit.*, give m. p. 193·5—194·5°, $[\alpha]_D^{28}$ + 109°.

The 6-acetate, prepared in the usual manner and crystallized from methanol, had m. p. 199—201°, $[\alpha]_D^{20}$ +106° in $COMe_2$, $\lambda_{max.}$ 2360 Å (ε 13,600), $\nu_{max.}$ 1736 (acetate and 17-ketone), 1674 cm.$^{-1}$ (unsaturated ketone), and no free hydroxyl band (Found: C, 73·25; H, 8·25. Calc. for $C_{21}H_{28}O_4$: C, 73·25; H, 8·2%) (Davis and Petrow, *loc. cit.*, give m. p. 200° for this substance, then believed to be the 3-acetoxy-Δ^4-6-ketone; Balant and Ehrenstein, *loc. cit.*, give m. p. 201—201·5, $[\alpha]_D^{27}$ +111°; Ehrenstein, *J. Org. Chem.*, 1941, **6**, 626, gives m. p. 174—176°, $[\alpha]_D^{27}$ +153·5° in $COMe_2$, for a product now known to be the 6α-isomer).

Androstane-3 : 6 : 17-*trione* (VIII*d*).—This was prepared by heating under reflux 6β-hydroxyandrost-4-ene-3 : 17-dione (0·3 g.) and potassium hydroxide (0·3 g.) in methanol (14 c.c.) and water (1·5 c.c.) for 30 min. After crystallization from methanol–ether, it had m. p. 192—193°, $[\alpha]_D^{20}$ +72°, no high-intensity absorption in the ultra-violet, $\nu_{max.}$ 1736 (17-ketone), 1706 cm.$^{-1}$ (saturated ketone), but no free-hydroxyl band (Ushakov and Lyutenberg, *J. Gen. Chem. Russia*, 1939, **9**, 69, and Davis and Petrow, *loc. cit.*, give m. p. 191—192°).

Androst-4-*ene*-3 : 6 : 17-*trione* (VII*d*).—A suspension of 3β : 6β-dihydroxyandrost-4-en-17-one (V*d*) (1 g.; finely ground) in chloroform (100 c.c.) was heated under reflux with manganese dioxide (10 g.) for 8 hr. with stirring. The product ($\lambda_{max.}$ 2480 Å, ε 9200) was chromatographed on alumina (50 g.), and the fractions eluted with benzene were combined. Crystallization of this material from acetone–ether furnished the triketone (0·43 g.), m. p. 223—225°, $[\alpha]_D^{20}$ +43° in $COMe_2$, $\lambda_{max.}$ 2500 Å (ε 10,600), $\nu_{max.}$ 1736 (17-ketone), 1684 cm.$^{-1}$ (Δ^4-3 : 6-dione), but no free-hydroxyl band (Found: C, 76·15; H, 8·15. Calc. for $C_{19}H_{24}O_3$: C, 75·95; H, 8·05%) (Butenandt and Riegel, *Ber.*, 1936, **69**, 1163, give m. p. 216—217°, $[\alpha]_D^{22}$ +42° in $COMe_2$; Ushakov and Lyvtenberg, *J. Gen. Chem. Russia*, 1937, **7**, 1821, give m. p. 221—222°).

Androst-4-*ene*-3β : 6β : 17β-*triol* (V*e*).—3β : 6β-Diacetoxyandrost-4-en-17-one (IV*d*) (7·8 g.) in tetrahydrofuran (200 c.c.) was gradually added to a solution of lithium aluminium hydride (3·9 g.) in ether (200 c.c.). The mixture was heated under reflux for 30 min., the excess of reagent was decomposed by means of ethyl acetate, and the product was isolated by the sodium sulphate procedure (cf. Mancera, Rosenkranz, and Sondheimer, *loc. cit.*). Crystallization from acetone furnished the unsaturated *triol* (4·8 g., 78%), m. p. 213—216°. Further crystallization gave material with m. p. 220—222°, $[\alpha]_D^{20}$ +13° in dioxan, $\nu_{max.}$ (mull) free-hydroxyl band only (Found: C, 74·2; H, 9·8. $C_{19}H_{30}O_3$ requires C, 74·45; H, 9·85%).

6β-*Hydroxytestosterone* (VI*e*).—A suspension of the foregoing triol (V*e*) (1 g.; finely ground) in chloroform (100 c.c.) was shaken at room temperature for 24 hr. with manganese dioxide (10 g.). Crystallization of the product from methanol–ether furnished 6β-*hydroxytestosterone*

(0·48 g.), m. p. 217—218°, $[\alpha]_D^{20}$ +34°, $\lambda_{max.}$ 2360 Å (ε 13,800), $\nu_{max.}$ 1670 cm.$^{-1}$ (unsaturated ketone) and free-hydroxyl band (Found: C, 74·7; H, 9·15. $C_{19}H_{28}O_3$ requires C, 74·95; H, 9·25%).

The 6 : 17-*diacetate*, prepared in the usual manner and crystallized from ether–pentane, had m. p. 134—135°, $[\alpha]_D^{20}$ +26°, $\lambda_{max.}$ 2360 Å (ε 13,100), $\nu_{max.}$ 1736 (acetate) and 1674 cm.$^{-1}$ (unsaturated ketone) (Found: C, 71·2; H, 8·3. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%).

Lithium–Ammonia Reduction of 6β-*Hydroxytestosterone* (VI*e*) *to Testosterone* [with Miss M. VELASCO].—6β-Hydroxytestosterone (1 g.) dissolved in dry tetrahydrofuran (30 c.c.) was added dropwise to a solution of lithium metal (0·5 g.) in liquid ammonia (200 c.c.), with stirring. After another 15 minutes' stirring, *tert.*-butanol was slowly added until the blue colour of the mixture was discharged. The ammonia was allowed to evaporate, water was added, and the product was isolated with chloroform. Crystallization from acetone–hexane then furnished testosterone (0·47 g.), m. p. 152—153°, identified with an authentic sample by mixed m. p. determination and comparison of infra-red spectra. Under similar reduction conditions testosterone was reduced to 17β-hydroxyandrostan-3-one.

17β-*Hydroxyandrostane*-3 : 6-*dione* (VIII*e*).—A solution of 6β-hydroxytestosterone (0·30 g.) and potassium hydroxide (0·30 g.) in methanol (14 c.c.) and water (1·5 c.c.) was heated under reflux for 30 min. Crystallization from ether–pentane yielded 17β-hydroxyandrostane-3 : 6-dione (0·21 g.), m. p. 233—235°, no appreciable absorption in the ultra-violet, $\nu_{max.}$ 1700 cm.$^{-1}$ and a free-hydroxyl band. The substance proved to be identical (mixture m. p., infra-red spectra) with a sample (m. p. 235—236°) prepared by an independent method (Sondheimer, Kaufmann, Romo, Martinez, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 4712).

6-*Oxotestosterone* (VII*e*).—Androst-4-ene-3β : 6β : 17β-triol (V*e*) (1 g.) and manganese dioxide (10 g.) in chloroform (100 c.c.) were heated under reflux with stirring for 8 hr. The product ($\lambda_{max.}$ 2480 Å, ε 9200) was chromatographed on alumina (50 g.), and the fractions eluted with benzene–ether (4 : 1) were combined. Crystallization from acetone–ether furnished 6-oxotestosterone (0·45 g.), m. p. 212—213°, $[\alpha]_D^{20}$ − 53° in $COMe_2$, $\lambda_{max.}$ 2500 Å (ε 11,200), $\nu_{max.}$ 1684 cm.$^{-1}$ (Δ^4-3 : 6-dione) and a free-hydroxyl band (Found: C, 75·4; H, 8·65. Calc. for $C_{19}H_{26}O_3$: C, 75·45; H, 8·65%) (Butenandt and Riegel, *loc. cit.*, give m. p. 203—205°, $[\alpha]_D$ −58° in $COMe_2$). A mixture m. p. determination with androst-4-ene-3 : 6 : 17-trione resulted in a *ca.* 20° depression, thus showing that the saturated 17β-hydroxyl group had not been oxidized. In the above chromatogram a small amount of 6β-hydroxytestosterone could be isolated from the later fractions.

17α-*Acetoxy*-3β : 5α : 6β-*trihydroxypregnan*-20-*one* (II*g*).—The performic acid hydroxylation was carried out as described above for 3β-hydroxyandrost-5-en-17-one (I*d*), with 3β : 17α-diacetoxypregn-5-en-20-one (20 g.; Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3489), formic acid (120 c.c.; 90%), and hydrogen peroxide (20 c.c.; 30%). The precipitate after addition of water was heated under reflux with potassium carbonate (13 g.) in methanol (300 c.c.) and water (60 c.c.) for 30 min. under nitrogen. Most of the solvent was removed under reduced pressure, water was added, and the precipitated *tetrol monoacetate* (14·6 g.), m. p. 285—288°, was collected. The analytical sample, obtained by crystallization from methanol–ether, had m. p. 296—298°, $[\alpha]_D^{20}$ −23°, $\nu_{max.}$ (mull) 1736 (acetate), 1704 cm.$^{-1}$ (saturated ketone), and a free-hydroxyl band (Found: C, 67·35; H, 8·65. $C_{23}H_{36}O_6$ requires C, 67·6; H, 8·9%).

3β : 6β : 17α-*Triacetoxy*-5α-*hydroxypregnan*-20-*one* (III*g*).—The crude precipitated monoacetate (II*g*) (14·0 g.), acetylated as usual and crystallised from methanol, furnished the *triacetate* (14·1 g.), m. p. 163—165°, $[\alpha]_D^{20}$ −50°, $\nu_{max.}$ 1732 (acetate), 1700 cm.$^{-1}$ (saturated ketone), and a free-hydroxyl band (Found: C, 65·55; H, 8·45. $C_{27}H_{40}O_8$ requires C, 65·85; H, 8·2%).

3β : 6β : 17α-*Triacetoxypregn*-4-*en*-20-*one* (IV*g*).—To the above triacetate (14·0 g.), dissolved in pyridine (46 c.c.) and cooled in ice, thionyl chloride (4·6 c.c.) was added. After another 5 min. at 0°, water was added, and the solid product was collected and crystallized from acetone–hexane. The unsaturated *triacetate* (10·2 g.), m. p. 180—184°, thus obtained, was suitable for the subsequent step. A purified sample showed m. p. 195—196°, $[\alpha]_D^{20}$ −19° (Found: C, 67·9; H, 7·8. $C_{27}H_{38}O_7$ requires C, 68·35; H, 8·05%).

3β : 6β : 17α-*Trihydroxypregn*-4-*en*-20-*one* (V*f*).—The unsaturated triacetate (9·0 g.) was heated under reflux with potassium hydroxide (5·0 g.) in methanol (450 c.c.) and water (50 c.c.) for 1 hr. in nitrogen. Isolation in the usual manner and crystallization from methanol–ether yielded the unsaturated *triol* (4·7 g.), m. p. 266—268°, $[\alpha]_D$ +27° in dioxan, $\nu_{max.}$ (mull) 1700 cm.$^{-1}$ (saturated ketone) and a free hydroxyl band (Found: C, 72·1; H, 8·9. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·25%).

6β : 17α-*Dihydroxyprogesterone* (VI*f*).—A suspension of the unsaturated triol (1 g.; finely

ground) in chloroform (100 c.c.) was shaken with manganese dioxide (10 g.) at room temperature for 24 hr. Crystallization of the product from methanol–ether furnished 6β : 17α-dihydroxyprogesterone, m. p. 254—256°, $[\alpha]_D^{20}$ +10°, $\lambda_{max.}$ 2360 Å (ε 12,800), $\nu_{max.}$ (mull) 1700 (saturated ketone), 1670 cm.$^{-1}$ (unsaturated ketone), and a free-hydroxyl band (Found : C, 73·05; H, 9·0. Calc. for $C_{21}H_{30}O_4$: C, 72·8; H, 8·75%) (Meister *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 416, give m. p. 250—252°, $[\alpha]_D^{23}$ +4°, +6°).

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The Heats of Dissolution and the Optical Rotatory Dispersion of 1 : 2-*Diphenylethanol.*

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The heats of dissolution of 1 : 2-diphenylethanol in selected solvents have been determined. Correlation of these measurements with the optical rotatory dispersion of the substance has been attempted. The measurements tend to support the view that the rotatory dispersion of the alcohol may largely be explained in terms of the " structure " of the solution. The use of a thermistor in a bridge circuit as a thermometer in a semimicro-calorimeter is described.

GERRARD and KENYON (*J.*, 1928, 2564) examined the rotatory dispersion of 1 : 2-diphenylethanol in various solvents in the visible spectrum at room temperature, and also the variation of the dispersion of the homogeneous substance with temperature. Although they were unable to examine the homogeneous substance below 60° (m. p. 67°), if their results are extrapolated to room temperature it will be seen that the values obtained are very similar to those observed in ethyl-alcoholic solution. This suggests that the two systems may be similar in the origin of their dispersion and that the " structure " of the solution is one of the major factors determining the dispersion. Since hydrogen-bridge formation is clearly the most likely cause of such liquid " structure " it was decided to measure the heats of dissolution or dilution of 1 : 2-diphenylethanol in the same solvents. In view of the small quantities of the substance then available it was necessary to use a semimicro-calorimeter which yields results of a moderate accuracy.

EXPERIMENTAL

Thermometer.—A " Stantel " thermistor, type F2311/300, was used in conjunction with a bridge circuit as shown in Fig. 1. The apparatus consisted of a rotary-type Post Office box combined with a rotary potentiometer (resistance 60 ohms) of Admiralty " Inpot " A.C. pattern. A 50,000-ohms resistance was used in series with the 2-volt accumulator to minimise the heating effect of the thermistor, which is otherwise noticeable with the small volumes used in these experiments. The galvanometer (Tinsley 4500H) had a sensitivity of 200 mm. per microamp. at 2 metres. At room temperature the sensitivity of the thermistor with the above equipment was about 0·0025°. It was calibrated throughout the range against a Beckmann thermometer.

Heating Circuit.—See Sturtevant, " Technique of Organic Chemistry," Interscience Publ., New York, Vol. I, " Calorimetry," 1945, p. 331.

Heater.—" Minalpha " wire (35 S.W.G.) was wound on a glass tube forming a duct for the stirrer. The stirrer guide was sealed at the top with a gas-tight seal to prevent " pumping." The resistance of the heater was about 10 ohms; it dissipated about 2 watts. A much larger wattage is desirable but was not feasible with the potentiometers available.

Pipette.—A special " self-emptying " pipette with a Soxhlet-type syphon was used [Fig. 2*a*]. The pipette was operated by a plunger in such a way that no air was drawn in from outside the calorimeter. The most satisfactory form of plunger from the chemical point of view was a loop

formed in a stainless-steel wire which was then twisted to form a handle. A pad of cotton wool was worked into the loop.

Mode of Operation of the Calorimeter.—The calorimeter was charged with the solid material. The pipette was filled with solvent and weighed, with covers over the holes X and Y [Fig. 2*a*] and then placed in the calorimeter. The stirrer was started, and the whole apparatus allowed to reach a steady temperature. The plunger was then depressed, and the temperature decrease read. The cotton-wool plug was moistened with solvent, after which it acted as an efficient seal, and the plunger was not allowed to make contact with the body of the solvent. The pipette and any remaining solvent were re-weighed at the end of the experiment.

Accuracy.—The accuracy obtained in the determination of the temperature decrease on dissolution was 1% or better, since with the dilute solution used in these experiments the dissolution was virtually instantaneous when compared with the rate of heat loss through the walls of the calorimeter. In other experiments, where an attempt was made to determine heats of dilution directly, much more concentrated solutions were required initially; with these the accuracy was much less owing to the time taken for the solute to dissolve. The actual temperature changes occurring on dilution can, however, be measured very accurately owing, again, to their instantaneous nature. In experiments made to determine the heat equivalents of the calorimeter and contents, however, the accuracy was rather less than in the other determination, being 3—5%, owing to the low power available which results in a relatively large correction for heat losses.

FIG. 1.

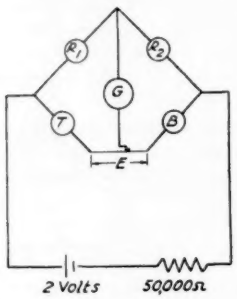

FIG. 1. B = Balancing resistance; E = rotary potentiometer; G = galvanometer; R_1 and R_2 = ratio arm resistances; T = thermistor.

FIG. 2*a*.

FIG. 2*a* (scale 1 : 3). *Pipette.*

W = Cotton-wool plunger; X and Y = apertures; Z = Soxhlet syphon.

FIG. 2*b*.

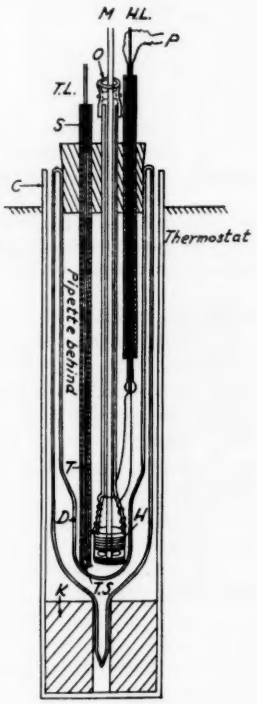

FIG. 2*b*. *Calorimeter, partly sectional.*

C = copper jacket; D = Dewar flask; H = heater; $H.L.$ = heater leads; K = cork support; M = drive from motor (0·05 h.p. fitted with 40-watt resistance and a brake); O = oil seal; P = potential leads; S = wax seal; T = thermistor; $T.L.$ = thermistor lead; $T.S.$ = thermistor shield.

The 1 : 2-diphenylethanol used was kindly supplied by Dr. Gerrard; recrystallised from ethyl ether and light petroleum, it had m. p. 66—66·5°.

Solvents.—These were fractionally distilled, dried as follows, and redistilled immediately before use. Drying agents: for carbon disulphide, phosphoric oxide; for carbon tetrachloride, chloroform, and acetone, calcium chloride; for ethyl alcohol, diethyl phthalate and sodium. Benzene of recrystallisable grade was purified by freezing.

Discussion of Results

Comparison of the values of the optical rotatory power and the heats of dilution (as measured by ΔH—L, where ΔH = the heat of dissolution to give a dilute solution and L = latent heat of fusion of the solute) of solutions of 1 : 2-diphenylethanol suggests that solvents may be classified into three groups so far as their interaction with this substance is concerned. For ethyl-alcoholic and acetone solutions ΔH—L is small, as was to be expected. The heat of dilution is approximately the same in the benzene, carbon disulphide, and carbon tetrachloride solutions at ~5·4 kcal./mole. The pyridine solution, on the other hand, shows a positive heat of dilution, and chloroform is anomalously placed. The rotatory dispersion of the chloroform solution makes it likely that there is a slight evolution of heat on dilution owing to combination with the solute, since the magnitude of the heat of dilution in chloroform is less than that observed in benzene, carbon disulphide, and carbon tetrachloride, where it may be assumed that no new " bonds " are formed during the dilution process. This behaviour is in conformity with other work that shows chloroform to have a tendency to dipolar association or the formation of other weak linkages in excess of that shown by solvents such as carbon tetrachloride (*e.g.*, Zellhoefer, Copley, and Marvel, *J. Amer. Chem. Soc.*, 1938, **60**, 1337; Macleod and Wilson, *Trans. Faraday Soc.*, 1935, **31**, 596; Le Fèvre, *ibid.*, 1937, **33**, 207).

Table 1

Thermostat temperature 25°. In each measurement 10 c.c. of solvent were added to 1 g. of solute, giving a concentration of 2—5 moles %.

Solvent	Dielectric constant	$[\alpha]_{4358}$ *	$[\alpha]_{5461}$ *	ΔH, kcal./mole	ΔH, Joules/mole	$\Delta H - L$, kcal./mole	$\Delta H - L$, Joules/mole
C_5H_5N	12·3	− 14·5°	−11·00°	−2·73	−11·4	+1·5	+ 6·3
$CHCl_3$	4·8	− 12·02	− 9·71	−7·5	−31·4	−3·3	−13·8
CS_2	2·6	− 9·00	− 8·15	−9·5	−39·8	−5·3	−22·2
C_6H_6	2·3	− 0·20	− 3·00	−9·4	−39·3	−5·2	−21·8
CCl_4	2·2	+ 6·90	+ 1·00	−9·9	−41·4	−5·7	−23·9
$COMe_2$	20·7	+ 44·63	+22·10	−5·8	−24·3	−1·6	− 6·7
EtOH	24·3	+120·8	+64·9	−5·6	−23·4	−1·4	− 5·9
Homog. extr'd. ...	—	+120	+67	—	—	—	—

$L^{30°} = -4·6$ kcal./mole (19·3 joules/mole).
$L^{27·7°} = -4·3$ kcal./mole (18·0 joules/mole).
$L^{25°}$ (by extrapolation) $= -4·2$ kcal./mole (17·6 joules/mole).
* The rotatory powers are from Gerrard and Kenyon (*loc. cit.*).

A qualitative correlation can be seen between the heats of dilution (as measured by $\Delta H - L$) and the magnitude of the rotatory powers, and particularly the rotatory strengths of the shorter wave-band corresponding to the sum of C–OH, C–C, and C–H absorption. The small negative value of the heat of dilution of the ethyl-alcoholic and acetone solution suggests that the heat of formation of the solute–solute and solvent–solvent " bonds " may be less than that of the solute–solvent " bonds." If the value of ΔH for the heat of dissolution of 1 : 2-diphenylethanol in ethyl alcohol is subtracted from that of the heat of dissolution in benzene a value of 4 kcal. per mole is obtained, whilst $\Delta H - L$ for the benzene solution yields 5·4 kcal. per mole for the energy required to overcome the intermolecular forces in the alcohol, compared to the 3 kcal./mole for the hydrogen-bridge bond in methanol (Redlich and Kister, *J. Chem. Phys.*, 1947, **15**, 849).

The plot of $[\alpha]$ against λ for the homogeneous material at 60° deviates from that of a *simple* dispersion curve by less than the experimental error, so it is not surprising that an attempt to derive a two-term equation from four experimental points was unsuccessful. On the other hand, the method of deriving a two-term Drude equation by the use of approximately known absorption frequencies of the molecule and two experimental points yields the results given in Table 2.

The justification of this method lies in the obvious " complexity " of the dispersion (Lowry, " Optical Rotatory Power," Longmans Green, 1935, p. 124) and in the implication of the one-electron theory (Condon, *Rev. Mod. Phys.*, 1937, **9**, 432) that most electronic transitions will contribute to the activity of the molecule.

In the carbon disulphide, benzene, and chloroform solutions the visible region of the spectrum includes the " sensitive " region of the dispersion. Hence, widely varying dispersion ratios are obtained together with the appearance of discontinuity. An analysis of the rotatory powers into rotatory strengths shows that continuity does, in fact, exist throughout the range of solvents.

It may be argued that in the case of the ethyl-alcoholic and acetone solutions the system contains an element of " structure " lacking in the other cases and that the rather high

TABLE 2

$[\alpha]_\lambda = p/(\lambda^2 - \lambda_1^2) + q/(\lambda^2 - \lambda_2^2)$, $\lambda_1 = 0{\cdot}25\mu$ and $\lambda_2 = 0{\cdot}15\mu$ being taken as very approximate wave-lengths for the benzenoid and hydroxyl bands and the $[\alpha]$ values being used for $\lambda = 0{\cdot}5461\mu$ and $\lambda = 0{\cdot}4358\mu$.

Solvent	Temp.	p	q	Solvent	Temp.	p	q	ΔH (kcal./mole)
Homog.	125°	6·94	6·33	C_5H_5N.....	20°	4·59	8·40	−2·75
,, ...	115	7·32	6·16	$CHCl_3$	20	4·60	8·05	−7·5
,, ...	100	8·58	6·48	CS_2	20	4·58	7·53	−9·5
,, ...	90	9·97	5·92	C_6H_6	20	5·50	7·26	−9·4
,, ...	80	9·32	5·28	CCl_4	20	6·86	7·86	−9·9
,, ...	70	10·29	4·98	$COMe_2$ ...	20	9·58	5·10	−5·8
,, ...	60	11·05	4·16	EtOH	20	17·77	3·11	−5·6

values of the rotatory power observed in these solvents are due to the " tying " of the active molecule in one configuration. This is in conformity with the finding, by Kauzman, Walter, and Eyring (*Chem. Reviews*, **1940**, **26**, 380) among others, that ring formation increases the rotatory power approximately ten-fold. This simple picture becomes somewhat blurred when the dispersion is examined, since it is shown below that, whilst the rotatory strength of the phenyl band is increased by the " partial lattice " formation, that of the hydroxyl band is decreased. According to the polarisability theory of rotatory power (Kirkwood, *J. Chem. Phys.*, 1937, **5**, 479, and particularly Bernstein and Pedersen, *ibid.*, 1949, **17**, 888) the rotivity, Ω, due to an asymmetric carbon group, as in *sec.*-butyl alcohol, may be considered as being due to two rotivities of opposite sign and a third of lower power corresponding to the different configurations about a single bond ($\Omega_1 + \Omega_2 + \Omega_3 = 0$). The observed rotatory power $\{[\alpha] = [\Omega](n^2 + 2)/3\}$ then depends on the proportion of each configuration present. If it could be shown that these different configurations have different optically active absorption frequencies then restriction of rotation, and of configuration, would be sufficient in itself to explain the observed dispersion of 1 : 2-diphenylethanol. On the other hand if, as seems likely, the absorption frequencies are approximately the same, then the dispersion must be explained in other terms.

In the case of the pyridine solution where a solute–solvent complex is apparently formed, some difference in the absorption from that of the simple molecule is to be expected, and possibly associated with it some change in the dispersion also. The method of calculation of the rotatory strengths used above makes it possible that the variation in the rotatory strengths shown in Table 2 is really to be attributed to a change in the frequency of the absorption band. However, if the increase in the rotatory strength of the shorter wave-band in going from benzene to pyridine solution is to be attributed entirely to this cause, the wave-band would have to be shifted some 600 Å towards the red. In chloroform solution the corresponding shift would be 400 Å. Neither of these shifts seem reasonable. Furthermore, a shift in the absorption wave-length would not account for the variation between alcoholic and benzene solutions. It may be noted that there is some correlation between the rotatory strengths and heats of solution of 1 : 2-diphenylethanol and the dielectric constant of the solvent. This relationship may be expected to be rather that between two effects with the same cause, than that between cause and effect. It is therefore necessary to attribute the variation of the rotatory strengths largely to the other factor which may affect them, *viz.*, the symmetry of the molecule or group (Condon, *loc. cit.*).

In the discussion of the effects of configurational changes in an optically active molecule on the symmetry of the field in which its electrons " move " it is convenient to consider the effect of these changes in an analogous model which does not contain an asymmetric

centre, since it is a reasonable assumption that symmetry changes occurring in this case may be superimposed upon the asymmetry of the active molecule. If the active 1 : 2-diphenylethanol molecule is included in a hydrogen-bridge network structure the symmetry of the O–H group may be considered to be increased, whereas the formation of a complex between the hydrogen of the hydroxyl group and the nitrogen of the pyridine molecule may be considered to increase the dissymmetric field in which the optical electrons of the hydroxyl group move. The imprecise use of the terms element of symmetry or increase in the dissymmetry is clearly to be deprecated—they are used here for want of better terms. As an example of their implication in this case, if the hydrogen-bridge structure were to be such that the O–H–O bonds were of equal length, then a new element of symmetry would definitely be introduced into a hydroxyl group : it would receive a diad axis. Though the lengths of the bonds in O–H–O are not generally considered to be equal (Davies, *Ann. Reports*, **1946**, **43**, 14) the dissymmetry of the field introduced by this non-symmetry of bond length may be slight compared with the general gain in the symmetry of the field accompanying the association.

It appears from a model that the large value of the rotatory strength of the 2500 Å band of the homogeneous substance at the lower temperatures and of the alcoholic solution at 20° must be connected with a tendency of the phenyl groups to orientate themselves as nearly parallel to one another as possible. In the *trans*-phenyl position much closer packing appears to be possible than in the *cis*-phenyl position. In 1 : 2-diphenylethane the *cis*-phenyl position has two planes of symmetry whereas in the *trans* there is one plane and a centre. The non-asymmetric remainder of the 1 : 2-diphenylethanol molecule might therefore be considered to have rather similar symmetry from the point of view of optical activity in either *cis*- or trans-position. The greatest dissymmetry will be shown by two intermediate configurations about the central C–C bond with approximately equal and opposite contributions to the rotatory strengths ; these are, however, unlikely in a hydrogen-bonded structure for spatial reasons. The most probable configuration in the close-packed state appears to be a *trans*-phenyl position in which the rotation of the phenyl groups is restricted owing to close packing, and the central bond of the ·CH(OH)·CH_2· group is twisted out of the plane of the phenyl groups, thus removing both a plane and a centre of symmetry. This element of dissymmetry will be superimposed upon the dissymmetry of the remainder of the molecule, giving a higher rotatory strength to the phenyl band, and its contribution will diminish as freedon of rotation is increased with rise of temperature. It is noteworthy in connection with the general symmetry of the substance that its melting point is some 20° below what might be expected by analogy with the simple ethane derivatives.

Though it may be considered that dissymmetry is not a quantity variable by degree but a quality capable of difference only in kind, it can also be argued that the variation of rotatory strengths with change of structure is, in part at least, a measurement of dissymmetry. That this is so follows from the fact, demonstrated above, that the variation of rotatory strengths with changed conditions cannot be accounted for purely in terms of the strengths of the electronic binding which would be reflected in the absorption frequencies of the molecule, nor is it usual for solvent effects to have a marked influence on the intensities of the absorption of the system. The changes in the rotatory strengths must therefore involve a change in the structure and symmetry of the system. Though there may be other ways of explaining the rotatory dispersion of 1 : 2-diphenylethanol, a satisfactory qualitative picture is obtained in this way.

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Surface Films of Phenolic Compounds.

By A. J. G. Allan and J. H. Schulman.

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An investigation of the surface structure of di- and poly-phenols has been undertaken by the Langmuir trough technique, concentrated ammonium sulphate solutions being used to make the compounds form insoluble monolayers.

The diphenols form hair-pin structures when the hydrocarbon chain joining the phenolic group contains more than three methylene groups. There is an analogy between melting points of the compounds and their monolayer stability.

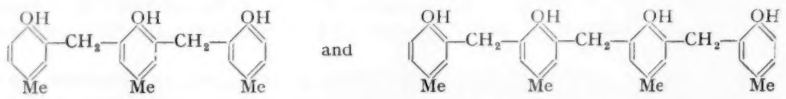
The polyphenols form gel films in which the structure of the molecule is such that one phenolic group is oriented underneath the array of the polyphenolic chain.

The adsorption of the diphenols from their aqueous solution on amine monolayers has been investigated.

Concentrated ammonium sulphate solutions have recently been used to stabilise surface films of otherwise water-soluble copolymers (Allan and Alexander, *Trans. Faraday Soc.*, 1950, **46**, 316). Hence it seemed possible that polypolar compounds used for interaction with monolayers when injected into a dilute aqueous substrate might themselves give stable vaporous films on concentrated salt solutions. In the experiments described below the surface behaviour of a series of di- and poly-phenols was examined and compared with the interaction of the diphenols with amine monolayers.

Experimental

Materials.—The preparation of an increasing chain series of di- and poly-phenols has been described in detail by Pepper (Ph.D. Thesis, Cambridge, 1941) and we are indebted to him for the gift of samples. The polynuclear phenols were formed by repetition of the phenolic nucleus, the units being joined by a CH_2 link, thus :



For convenience these are referred to as the " trimer " and " tetramer " and were prepared by Pepper, modifying the methods of Koebner (*Z. angew. Chem.*, 1933, **46**, 251) and Megson and Drummond (*J. Soc. Chem. Ind.*, 1930, **49**, 245). The diphenol series was formed by increasing the length of the hydrocarbon chain between two phenolic nuclei, *viz.*,

$$p\text{-HO}\cdot C_6H_4\cdot[CH_2]_n\cdot C_6H_4\cdot\text{OH-}p,$$

where n varies from 0 to 6. The first two members of the series are well known and were prepared by standard methods. The third member, *pp'*-dihydroxydibenzyl ($n = 2$) was prepared by reduction of anisil followed by demethylation with hydrobromic acid. The fourth member, 1 : 3-di-*p*-hydroxylphenylpropane ($n = 3$), was prepared *via pp'*-dimethoxychalkone, which was reduced to di-*p*-methoxyphenylpropane and the latter demethylated by aqueous acetic–hydrobromic acid.

The di-*p*-hydroxyphenylbutane was synthesised by using succinic anhydride and introducing the *p*-methoxyphenyl nuclei one at a time.

To prepare the sixth member, 1 : 5-di-*p*-hydroxyphenylpentane, Pepper first condensed anisaldehyde with acetone and obtained 1 : 5-di-*p*-methoxyphenylpentan-3-one by hydrogenation. This was reduced to 1 : 5-di-*p*-methoxyphenylpentane and the latter demethylated. The seventh member, 1 : 6-di-*p*-hydroxyphenylhexane was prepared by making dianisoylbutane from adipyl chloride and anisole and reducing it to 1 : 6-di-*p*-methoxyphenylhexane which was demethylated with aqueous acetic–hydrobromic acid.

The diphenols were soluble in aqueous ethanol and the polynuclear phenols dissolved in 10% alcohol–benzene. The solutions for spreading were *ca.* 0·5 mg./ml. and the substrates were solutions of " AnalaR " quality ammonium sulphate.

The interaction of the increasing chain series with octadecylamine hydrochloride films was examined. The amine films were spread from benzene–alcohol mixtures, and the phenolic compounds for injection were prepared in M/50-sodium hydroxide at concentrations of 0·5 mg./ml. In these experiments the substrates were M/50-sodium hydroxide and M/250-borate buffer.

Method.—The apparatus used was a Langmuir trough as modified by Alexander, Glazer, and Saggers (unpublished experiments) for automatic recording of surface pressure–area curves. The optical lever arrangement had a light spot indicating the surface pressures on a paper-covered drum. The drum rotated as the film was compressed, the steady rate of compression being controlled by an oil-immersed piston. It was found convenient to hold a pencil point on the light spot as the drum rotated. Calibration was carried out by marking the light spot for various small weights in the scale pan, with the drum stationary and a clean surface between the barriers and behind the float.

After the film had been spread the plunger was allowed to fall slowly in the oil cylinder, the speed of compression being regulated within wide limits. The rate of compression was usually about 3 cm. of trough length per min. but variation of the rate did not affect the results within reasonable limits. The films were spread from an all-glass micrometer syringe.

The phenolic substances were injected under the surface of the amine films by a pipette which was moved across the trough as the solution was expelled, directing the flow under the film from behind the barrier, thus avoiding contact with the film.

Results and Discussion

(i) *Diphenols on Concentrated Ammonium Sulphate Solution.*—The lowest members of the homologous series dissolved even in saturated ammonium sulphate and stable films could only be obtained with the three highest members ($n = 4$, 5, and 6). These were spread on 37·5% w/w ammonium sulphate solution and the highest member of series ($n = 6$) could be spread on 20% w/w solution. The Π–A curves shown in Fig. 1 are more expanded than the curves of $\omega\omega'$-diresorcinyldecane obtained by Adam (*Proc. Roy. Soc.*, 1928, *A*, **119**, 639). The curves are seen to be similar, except in the values of the collapse pressures. These, together with the minimum areas at collapse are shown below.

No. of CH_2 groups, n	Minimum area at collapse pressure, Å²/molecule.	Collapse pressure, dynes/cm.	M. p. of crystal
4	50	15·2	155°
5	48	27·0	101
6	53	13·3	142

If it is assumed that the area at collapse is the minimum area of close packing on the surface, it appears that both phenyl nuclei remain in the surface since the areas are approximately equal and equivalent to twice the area of a benzene ring at zero compression, *ca.* 24 Å². From molecular models it seems that there is little steric hindrance to compression of the molecule from a flat position to one where the phenyl rings are vertical to the surface and close packed with the methylene groups in the air phase. There is seen to be good agreement between collapse areas of the various stable compounds.

A further interesting point is shown in the above Table. The collapse pressure of the $n = 5$ compound is almost twice that of the other two. This is believed to be closely related to the alternate melting point phenomenon of homologous series in three dimensions. Several authors (see Smith, *Ann. Reports*, 1938, **35**, 255) have attributed this odd–even alternation in melting point to the ease of packing in the crystal form, and it is suggested that the collapse pressures of the diphenols are also functions of the ease of packing in the crystal form.

(ii) *Polyphenols on Concentrated Ammonium Sulphate Solutions.*—The two polynuclear phenols gave stable, fairly condensed, gel-like films on 37·5% w./w. ammonium sulphate solution, the Π–A curves being shown in Fig. 2. Although these films were not studied in detail, the areas at zero surface pressure and the minimum areas at collapse are noteworthy.

It would appear that each compound is initially fixed with all its phenolic nuclei in the surface. As these are packed more closely, there is a reorientation of the molecule so that one of the phenolic nuclei leaves the surface. At first sight this seems surprising, but consideration of steric effects with models shows that it is possible to pack the polar groups very closely together with one phenolic nucleus almost flat in the surface and one tilted so that the third is above the first and not contributing to the molecular area. This can be visualised as a box-like formation parallel to the surface, the fourth phenyl group being parallel to the second. Although this concept requires to be confirmed by surface-potential measurements it seems the only way to explain the reproducible and closely corresponding Π–A curves.

(iii) *Interaction of Diphenols with Amine Monolayers.*—Films of octadecylamine hydrochloride on M/250-borate (pH 9) and M/250-sodium hydroxide (pH 12) were not affected by solutions of the *pp'*-dihydroxydiphenyl, although the 1 : 6-di-*p*-hydroxyphenylhexane showed a slow but stable interaction with both substrates. The Π–A curves are shown in Fig. 3. Pepper (*loc. cit.*) prepared both series of compounds for injection under amine

FIG. 1. II–A *curves for diphenols on concentrated ammonium sulphate solutions.*

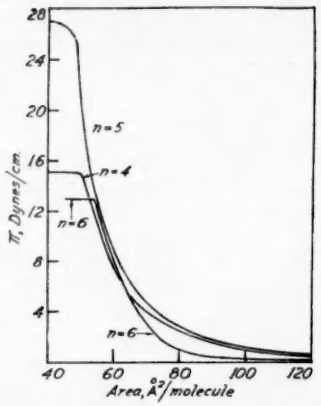
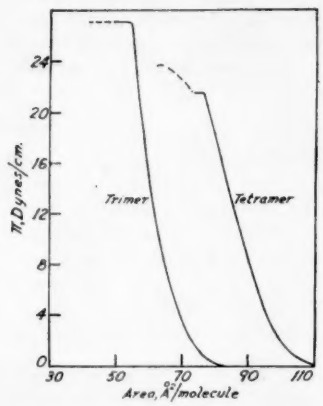


FIG. 2. II–A *curves for polyphenols on* 37·5 w/w *ammonium sulphate solutions.*



monolayers to examine the effect on the films of the number and spacing of the polar groups and the size of the non-polar portion. Although he was unable to carry out detailed experiments he stated that there was considerable penetration of the amine film by all the compounds. Unfortunately, his experiments were complicated by injecting high concentrations of the diphenol (*ca.* 10 mg./l.) under the film so that thick polylayers of the diphenols were formed on each side of the barrier. In these experiments the concentration of the diphenol injected was reduced to a final value of 1 mg./l. in the substrate and a more dilute buffer was used. No film formation of the diphenol was observed on the surface of the substrate behind the barrier. The marked interaction of the 1 : 6-di-*p*-hydroxyphenylhexane is shown in Fig. 3, and has interesting characteristics. Although some two hours are required before the interaction is complete, thereafter the Π–A curve is reproducible on compression and re-expansion several times. A stable association seems to be formed between the amine and the diphenol, so that the latter is held by the amine in the surface and at the same time the octadecylamine-head groups are kept apart by the diphenol against their hydrocarbon chain cohesion. Cockbain and Schulman (*Trans. Faraday Soc.*, 1939, **35**, 716) studied the interaction of amines with organic acids and showed that the concentrations of organic acid in the substrate giving the same amount of change in the Π–A characteristics depend greatly on the nature of the non-polar residue. Thus, increasing the non-polar portion of the diphenol by 6 methylene groups results in marked interaction with the amine for the same concentration of diphenol in the substrate. This is analogous to the

results of Cockbain and Schulman with azelaic acid and thapsic acid, $[CH_2]_n(CO_2H)_2$, $n = 7$ and 14, respectively.

The markedly expanded film in the experiments on M/250-borate buffer [curve (*a*), Fig. 3] shows a sharp kink at an area of 27 Å^2/molecule and a pressure of 24 dynes/cm. This area at the kink point is considered to confirm the belief that the diphenol can take up a hairpin-like structure on the surface. In this case it is thought that the diphenol is hooked under the amine film with the non-polar portion forced into the substrate. When the area of the amine film reaches 27 Å^2/molecule, the diphenol " sub-film " is close packed, *i.e.*, one diphenol molecule is attached beneath two amine groups. Below 27 Å^2/molecule

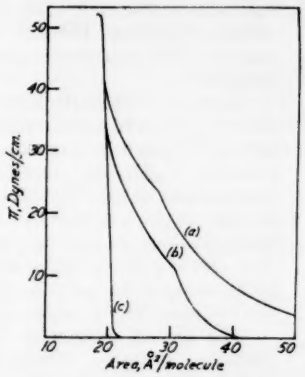


FIG. 3. II–A *curves for octadecylamine hydrochloride with* 1 : 6-*di*-p-*hydroxyphenylhexane injected into substrate :* (a) M/250-*borate buffer*, pH 9; (b) M/50-*sodium hydroxide*, pH 12.

the association of the amine and the diphenol is disrupted and the diphenol is squeezed partly into the substrate until the amine film itself is close packed (*c*).

When M/50-sodium hydroxide is substituted for the M/250-borate buffer the kink point occurs at a slightly larger area, *ca.* 32 Å^2/molecule, and at a lower pressure, 9 dynes/cm. This may be due to salt formation of the phenolic group with the alkali at the increased pH of the substrate.

Surface-potential measurements are clearly necessary to confirm the orientations suggested by the surface pressure–area curves. All the same, there is strikingly close agreement between the members of the diphenol series and between the two polyphenols. The interaction between the amine monolayers and " sub-film " of 1 : 6-di-*p*-hydroxyphenylhexane supports the suggestion that the diphenol can take up a hairpin-like structure at an interface.

DEPARTMENT OF COLLOID SCIENCE,
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Ajmaline. Part I.

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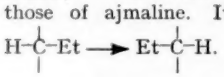
The most abundant alkaloid of *Rauwolfia serpentina*, Benth., namely, ajmaline, $C_{20}H_{26}O_2N_2$, has been further investigated.

On vigorous decomposition (soda-lime or zinc dust distillation) it affords *ind*-*N*-methylharman, carbazole, and simpler indole derivatives. A benzene nucleus represents the sole unsaturated group (hexahydroajmaline) and a dihydroindole structure is indicated by colour reactions and the ultra-violet absorption.

A group :N·CH(OH)· is recognised (*a*) by transformation of the oxime into a nitrile (infra-red and hydrolysis), (*b*) by study of *N*-methylajmaline (CO infra-red band) which by a series of processes can be converted into monodeoxyajmaline, $C_{20}H_{26}ON_2$ (:N·CH_2), and (*c*) by application of Huang-Minlon's modification of the Wolff–Kishner reduction process to ajmaline and some of its derivatives, whereby :N·CH(OH)· yields :NH CH_3· (deoxydihydroajmaline from ajmaline, deoxyoctahydroajmaline from hexahydroajmaline, and so on). This :N·CH(OH)· group confers properties on the base which are not those hitherto associated with carbinol-amines: *e.g.*, ajmaline is a strong base and the hydroxyl group can be acylated.

The second oxygen is also contained in a hydroxyl group (diacetylajmaline, infra-red absorption of deoxydihydroajmaline, etc.), and the stability of deoxyoctahydroajmaline towards chromic acid suggests that the second hydroxyl is tertiary—this point is not certainly established. On oxidation of deoxydihydroajmaline with chromic acid, a significant quantity of ethyl methyl ketone was obtained: this proves that the reduced base contains the group –CHMeEt and, as the *C*-Me value was notably increased on passage from ajmaline to deoxydihydroajmaline, ajmaline must contain :N·CH(OH)·CHEt.

Such a unit in the structure is strongly suggestive of a Woodward fission of ring E (yohimbine skeleton), and a consideration of congeneric alkaloids as well as the degradation to a harman derivative shows that ajmaline falls in the α(yohimbine) rather than the β(strychnine) class of indole alkaloids. A structure is tentatively advanced, but further work is necessary in order to determine the points of attachment of the second hydroxyl group, and carbon atoms numbered 2 and 3, in the benzene ring of the presumed phenylalanine progenitor. *iso*Ajmaline, obtainable from ajmaline by the action of heat or alkalis, and also of natural occurrence, affords a series of derivatives similar to those of ajmaline. It is regarded as a stereoisomeride of ajmaline:



Although more than forty *Rauwolfia* species have been described, *R. serpentina*, Benth. (syn. *Ophioxylum serpentinum*, Willd.) is the only one with a long history of medical use.

It is mentioned in the older Indian literature (Charaka) as a febrifuge, a remedy for snake-bites, and a cure for dysentery. Its reputation extended to Europe by 1690 (Rumphius) and in the "Herbarium Amboinense" (1741), it was stated that serpentina root "valet contra anxietatem." There is no mention of this hypnotic and sedative property in the older Indian literature but the drug has long been popularly used in Bihar as a hypnotic for children. Its most important action, in reducing the blood pressure, was established in 1931—1933 by Indian pharmacologists (Chopra, Gupta, and Mukherjee, *Indian J. Med. Res.*, 1933, **21**, 261; cf. *ibid.*, 1937, **24**, 1125; 1941, **29**, 763; 1942, **30**, 319; 1943, **31**, 71). The drug has acquired a reputation, especially in India, as a remedy for insomnia, hypochrondria, and even for some forms of insanity, and more recently the

intensification of the study of its chemistry and pharmacology has led to important results.

It had already been noted that extracts made from plants grown in Bihar were more active as a sedative than those originating in Dehra Dun, whereas the reverse was held to be true in respect of the treatment of insanity. This indicated the specific action of one or more variable constituents and it is now known that the roots contain at least fifteen different alkaloids. Recently the alkaloidal constituent (reserpine) claimed to be chiefly responsible for the sedative and hypertensive actions has been examined (Müller, Schlittler, and Bein, *Experientia*, 1952, **8**, 358. Full paper; Dorfman, Furlenmeier, Huebner, Lucas, MacPhillamy, Müller, Schlittler, Schwyzer, and St. Audré, *Helv. Chim. Acta*, 1954, **37**, 59). The pharmacology of the group has also been closely studied by Raymond-Hamet (*Compt. rend.*, 1935, **201**, 1050; 1939, **209**, 384, 599; *Compt. rend. Soc. biol.*, 1938, **129**, 462; 1939, **132**, 213).

A chemical investigation of *R. serpentina* was made by van Itallie and Steenhauer (*Arch. Pharm.*, 1932, **270**, 313) who isolated rauwolfine, $C_{21}H_{26}O_2N_2$, and two other bases, from the roots. Rauwolfine on distillation with zinc dust in a stream of hydrogen was stated to yield ammonia, scatole, quinoline, and carbazole, but these claims were substantiated only by a few colour reactions and ultra-violet spectra.

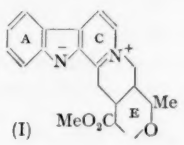
Approximately simultaneously, Siddiqui and Siddiqui (*J. Indian Chem. Soc.*, 1931, **8**, 667; 1932, **9**, 539; 1935, **12**, 37; R. H. Siddiqui, Inaug. Diss., Aligarh, 1934) made important contributions and isolated ajmaline, $C_{20}H_{26}O_2N_2$, and five other bases from the same botanical material.

There can be no doubt but that ajmaline is the rauwolfine of van Itallie and Steenhauer and the name rauwolfine should be reserved for the alkaloid, $C_{20}H_{26}O_3N_2$, isolated by Koepffli from *R. caffra*, Sonder (*J. Amer. Chem. Soc.*, 1932, **54**, 2412). This conclusion follows from a comparison of the properties of the rauwolfine of van Itallie and Steenhauer and the ajmaline of the Siddiquis as well as those of *iso*rauwolfine and *iso*ajmaline. R. H. Siddiqui (*op. cit.*) reproduces a sketch of a single crystal of rauwolfine hydrochloride made by Dr. L. H. Sitter (van Itallie and Steenhauer, *Pharm. Weekblad*, 1932, **14**, 341) which he states entirely agrees in form with his ajmaline hydrochloride.

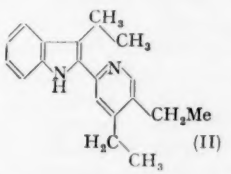
In our own investigations no base, $C_{21}H_{26}O_2N_2$, resembling ajmaline, $C_{20}H_{26}O_2N_2$, has been encountered. *iso*Ajmaline has been found by S. Siddiqui as a constituent of *R. serpentina* collected in the Dunn valley (*J. Indian Chem. Soc.*, 1939, **16**, 421) and this was accompanied by *neo*ajmaline, $C_{20}H_{26}O_2N_2$.

A specimen of *neo*ajmaline hydrochloride was kindly given to us by Dr. Siddiqui but we are unable to distinguish it from ajmaline with any certainty. One recrystallisation gave ajmaline hydrochloride and the m. p. 205—207°, quoted for *neo*ajmaline, is that of anhydrous ajmaline.

A survey of *Rauwolfia* and closely related genera of the apocynaceae shows that the most usual skeleton of their indole alkaloids is of α-type (yohimbine) rather than of β-type (strychnine).*



(I)



(II)

In particular a major alkaloid of *R. serpentina* is serpentine and a recent study (Schlittler and Schwarz, *Helv. Chim. Acta*, 1950, **33**, 1463; Bader and Schwarz, *ibid.*, 1952, **35**, 1594) has shown that this base is $C_{21}H_{22}O_3N_2$ (replacing the $C_{20}H_{20}O_3N_2$ of Siddiqui and Siddiqui), that it contains a methoxycarbonyl group, and that it yields alstyrine (II) on selenium dehydrogenation. The constitution (I) was proposed (*loc. cit.*) for serpentine, with reservations in regard to ring E. In any case the formation of alstyrine

* One of us (E. S.) has recently identified yohimbine itself as an alkaloid of *R. serpentina*.

(Karrer and Enslin, *Helv. Chim. Acta*, 1949, **32**, 1390; 1950, **33**, 100) demonstrates that serpentine is of α-type and reference to this fact is made in the sequel.

The *R. serpentina* roots used in our work were collected in India through CIBA (Bombay). The material has been worked up on a considerable scale and new methods have been developed in this connexion. A brief account of the isolation of ajmaline is included in the Experimental section, and one of us (E. S.) with his colleagues is engaged in a comprehensive study of the alkaloids contained in the other fractions, as well as of those of different *Rauwolfia* species.

In general, the work of Siddiqui and Siddiqui has been confirmed although the interpretation of their results must often be changed. For example, their dibromoajmaline is bromoajmaline hydrobromide. Ajmaline exhibits colour reactions characteristic of alkylated anilines with a free *p*-position and its ultra-violet absorption (see Figure) resembles that of many 2 : 3-dihydroindole derivatives. It is, for example, closely similar to that of hexahydro-9 : 11-dimethylcarbazole examined by M. F. Millson (Thesis, Oxford, 1951).

On catalytic hydrogenation it affords a perhydro-derivative showing no characteristic ultra-violet absorption or colour reactions.

The benzene nucleus is remarkably easily reduced and this led us in our earlier work to suspect the presence of a double bond. However, there is no unsaturation apart from that of the benzene ring.

On the convention that N(*a*) is attached to the benzene ring, N(*b*) is the basic nitrogen. Thus ajmaline metho-salts exhibit the usual colour reactions, proving that N(*a*) has not been quaternised. As regards the functions of the oxygen atoms we were at first inclined to the view that a semiacetal group ·O·CH(OH)·, was present (Mukherjee, Robinson, and Schlittler, *Experientia*, 1949, **5**, 215). This seemed to follow from the formation of ajmaline oxime, the power of ajmaline to reduce ammoniacal silver solutions, and the fact that ajmaline *appeared* to give a positive response in the Angeli–Rimini reaction for aldehydes. We have not, however, in later work established conditions under which this last test succeeds and we suspect the intervention of acetaldehyde, not on its own account, but as a link between ajmaline and the benzenesulphonylhydroxylamine.

This semiacetal hypothesis involved some special theory for diacetylajmaline, for example, that it contains $\geqslant$C·OAc and AcO·CH:C$<$. However, diacetylajmaline shows no infra-red absorption band corresponding to the latter unsaturated structure, nor one for :N·COMe. It is a weak base forming a N(*b*)-methiodide (colour reactions); its pK_a was found to be 4·9, which is close to that of *neo*strychnidine (4·6). It can be hydrolysed to ajmaline by acids or alkalis, or by treatment with lithium aluminium hydride, observations which tell against the assumption that :N·COMe is contained in the diacetyl derivative. Similar observations were made with diacetylhexahydroajmaline and it is very significant that this substance could be prepared not only by acetylation of hexahydroajmaline but also by catalytic reduction of diacetylajmaline.

It seems certain that ajmaline contains two hydroxyl groups, capable of acetylation. R. H. Siddiqui (*op. cit.*) found by Zerewitinoff's procedure two active hydrogen atoms in ajmaline dried at 100° and one after drying at 150°. We have examined the methanol compound, $C_{20}H_{26}O_2N_2,CH_4O$ and found three active hydrogen atoms.

Further experiments have confirmed the presence of a reducing group but it is now regarded as :N·CH(OH)·, though the carbinol-amine must be of a most unusual kind. The following three lines converge on this point.

(1) Ajmaline oxime hydrochloride, treated with acetic anhydride, acetic acid, and hydrogen chloride at room temperature furnished a salt, $C_{20}H_{25}N_3(OAc)_2,2HCl$. Alternatively this may be acetylanhydroajmaline dihydrochloride with 1AcOH of solvation. When treated with methanol and a little potassium hydroxide this salt gave a beautifully crystalline base, anhydroajmaline oxime, $C_{20}H_{25}ON_3$, which exhibits the characteristic infra-red absorption band for a –CN group (and absence of a CO frequency) and a band for OH or NH. On hydrolysis with concentrated hydrochloric acid it gave the salt, $C_{20}H_{26}O_3N_2,2HCl$, of an amphoteric base, as well as ammonium chloride. Lactamisation of this imino-acid was not found possible, probably because N(*b*) would be at the apex of a bridged-ring system in the hypothetical amide which would result. On reduction with

lithium aluminium hydride, anhydroajmaline oxime was reconverted into ajmaline, which is not itself reduced by this reagent. It is evident that ajmaline contains a latent aldehyde group which could on this evidence be ·O·CH(OH)· or :N·CH(OH)·. But on treatment with methyl iodide, anhydroajmaline oxime was converted into anhydro-*N*-methylajmaline oxime hydriodide, which was not a quaternary salt since its aqueous solution gave an immediate precipitate of a base on the addition of dilute ammonia. Hence anhydroajmaline oxime appears to be a secondary base and the group :N·CH(OH)· is indicated as present in ajmaline.

(2) When ajmaline was subjected to the Huang-Minlon modification of the Wolff–Kishner reduction method, it was converted in >90% yield into a deoxydihydroajmaline (pK_a 8·25; ajmaline, 8·15). Kuhn–Roth determinations show that ajmaline contains one *C*-Me group, and deoxydihydroajmaline two. The reduction product is also a secondary base: with methyl iodide it yields an *N*-methyl-hydriodide, giving a precipitate in aqueous solution with ammonia; it afforded an amorphous *N*-acetyl and a crystalline toluene-*p*-sulphonyl derivative (pK_a <2·5) which still exhibit the typical colour reactions showing that N(*a*) is not involved.

This evidence is almost conclusive in favour of the scheme:

$$:\overset{(b)}{N}\cdot CH(OH)\cdot \longrightarrow :\overset{(b)}{N}H \quad CH_3\cdot \longrightarrow :\overset{(b)}{N}\cdot SO_2\cdot C_7H_7 \quad CH_3\cdot$$

Hexahydroajmaline was similarly reduced to deoxyoctahydroajmaline, which base was also prepared by catalytic reduction of deoxydihydroajmaline.

(3) Ajmaline methiodide behaves on titration as the salt of a strong base of pK_a 9·2, rather than as a true quaternary salt. The glass obtained on distillation of this base gave a strong carbonyl band at 5·80 μ and a weak band at 5·92 μ, showing presence of a conjugated carbonyl group. In chloroform solutions the band at 5·80 μ became weak and that at 5·93 μ strong. This interesting behaviour is explicable on the hypothesis that :NMe and OHC· are present in the glass but that their approach for conjugation is hindered. This is facilitated by dissolution in chloroform (cf. Anet, Bailey, and Robinson, *Chem. and Ind.*, 1953, **22**, 944):

$$:N\cdot CH(OH)\cdot \longrightarrow :\overset{+}{N}Me\cdot CH(OH)\cdot \longrightarrow :NMe \quad OHC\cdot \longrightarrow :NMe\cdots \overset{H}{\underset{|}{C}}=O$$

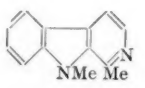
We were thus compelled to accept the carbinol-amine nature of ajmaline which was considered and rejected at an early stage because the base shows so little resemblance in its behaviour to other carbinol-amines, such as cotarnine or ψ-strychnine. For example, ajmaline is not reduced by zinc dust and boiling dilute hydrochloric acid and it forms *O*-acyl derivatives without fission. The base strength of ajmaline is much greater than would have been predicted.

The condensation reactions, occurring so readily in other cases, either do not occur or are difficult to interpret. Thus ajmaline forms a compound with methanol which is probably $C_{20}H_{26}O_2N_2$,MeOH. But it could be $C_{20}H_{25}O(OMe)N_2$,H_2O. It is proposed to devote further attention to this topic. With sulphur dioxide, a compound $C_{20}H_{26}O_2N_2$,H_2SO_3,H_2O was obtained and it is similarly difficult to determine whether this is truly the betaine of a sulphonic acid: $:N\cdot CH(OH)\cdot \longrightarrow :\overset{+}{N}H_2\,\bar{O}_3S\cdot CH(OH)\cdot$. It might be the hydrogen sulphite of the base. Neither ajmaline nor any of its derivatives responds to the test by *m*-dinitrobenzene and methanolic alkali. This we regarded as evidence that the group $:N\cdot CH(OH)\cdot C\overset{C}{\underset{C}{<}}C$ was present in the molecule. For reasons mentioned below we have now abandoned this deduction from negative evidence in favour of a different conclusion from positive evidence.

*iso*Ajmaline, which is produced from ajmaline by the action of heat or of hot alcoholic alkali, shows the same ultra-violet and infra-red absorption spectra as ajmaline and affords an entirely parallel series of derivatives. The substances are clearly stereoisomerides. Whereas deoxydihydro-*N*-methylajmaline could not be crystallised, the corresponding deoxydihydro-*N*-methyl*iso*ajmaline, $C_{21}H_{30}ON_2$, had m. p. 129—130°.

Although deoxyajmaline cannot be obtained by direct reduction of the base, we have made it indirectly, following methods used for the first preparations of *neo*strychnidine and *neo*strychnine. *N*-Methyl-*sec.*-ajmaline [:NMe(*b*) OCH·] was reduced by lithium aluminium hydride or potassium borohydride, and the product isolated as a hydriodide (:NHMe}I HO·CH_2·). This was converted by boiling aqueous hydrobromic acid into a Br quaternary salt (:$\widetilde{N}$Me·CH_2·), and the related chloride was pyrolysed to deoxyajmaline (:N·CH_2·).

Degradations of ajmaline were undertaken in the early stages of our work. Heating with soda–lime at 280—300° gave some indolaceous material, the Ehrlich reaction of which suggested β-substitution, also a little crude carbazole, recognised by colour tests, and as main product *ind-N*-methylharman (III). A new synthesis of this substance was effected, in that harman was methylated by treatment with potassamide and then methyl iodide in liquid ammonia solution. The :NMe which ajmaline contains is therefore :N(*a*)Me. Distillation of ajmaline over zinc dust in a stream of hydrogen at about 380° afforded *ind-N*-methylharman and carbazole in about equal amounts. In this case the carbazole could be purified and characterised. These results have been mentioned in a preliminary account (Mukherjee, Robinson, and Schlittler, *loc. cit.*). More recently we have found that the oxidation of deoxydihydroajmaline or deoxydihydro*iso*ajmaline with chromic acid affords



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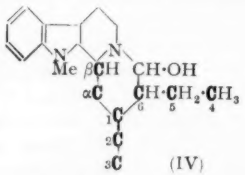


(IV)

ethyl methyl ketone. This enables us to write ·CHMeEt as a unit of the structure of deoxydihydroajmaline. Since the formation of the deoxydihydro-bases involves N–C fission and appearance of a new *C*-Me group, the only possibilities for ajmaline are (i) :N·CH(OH)·CH_2·CHMe· and (ii) :N·CH(OH)·CHEt·. For purposes of further discussion we adopt (ii) because it is in better accord than (i) with the usual indole-alkaloid skeleton and because it helps us to understand the ajmaline ⟶ *iso*ajmaline transformation. The latter is plausibly an inversion of the group –CHEt– brought about by its direct union with the potential aldehyde group.

A part structure (IV) can now be set down on the basis of *ind-N*-methylharman and ethyl methyl ketone. The carbon atoms in heavy type are those of a phenylalanine progenitor on Woodward's hypothesis of strychnine biogenesis and they are numbered accordingly (cf. *Nature*, **1948**, **162**, 155).

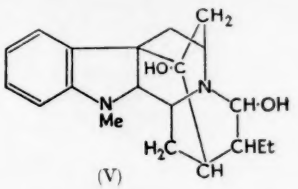
The second hydroxyl group of ajmaline is retained in deoxyoctahydroajmaline and it has been found that this substance can be recovered unchanged after treatment with chromic acid. This evidence, though not conclusive, tends to show that the hydroxyl group in question is tertiary. But this group is also resistant to thionyl chloride and several other reagents designed to replace it or to dehydrate the molecule. This behaviour recalls that of *apo*camphan-1-ol (Bartlett and Knox, *J. Amer. Chem. Soc.*, 1939, **61**, 3185) and it is probable that, as in this substance, the second (tertiary) hydroxyl group of ajmaline is at the apex of a bridged-ring structure and is protected from inversion replacement.

Accepting this for the present we find that the hydroxyl group and the two additional rings can be accommodated in the structure (V), which is provisionally advanced as the best representation of the chemistry of the alkaloid possible at this date.

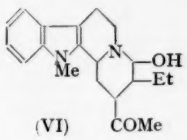
Biogenetically (V) could arise from (VI), or some such structure; and (V) gives a model in which the appearance of unsaturation between N(*b*) and CH(OH), *i.e.*, a group :$\overset{+}{N}$(*b*):CH·, is seen to be difficult—this may account for the unusual character of the :N(*b*)·CH(OH)· in ajmaline.

It remains to mention that A. Chatterjee and S. Bose have recently published a

discussion (*Experientia*, 1953, **9**, 254) of the structure of ajmaline which is based on our preliminary account together with some new facts. These authors claim to have observed 20% carbonyl absorption in the infra-red region (5·82 μ). The conditions of their experiments may be different from ours, but neither in Nujol suspension nor in chloroform solution have we seen such a band. It is of course quite in line with our views, but we have not found it. We are also unable to confirm the alleged bands at 7·24 μ (:CMe) and at 9·0 μ (ether bridge). The formula suggested by Chatterjee and Bose is one that we have considered and discarded. We had already disclosed (*loc. cit.*) the formation of *ind-N*-methylharman on drastic treatment of ajmaline; Chatterjee and Bose find that it is a product of dehydrogenation of ajmaline by selenium at 300°.



(V)



(VI)

Finally it should be mentioned that stereoisomerism due to the secondary alcoholic group has not yet been observed. The cause could be either great lability or great stability and we propose to examine carefully this aspect of the chemistry of the base.

Experimental

Isolation of Ajmaline.—The ground bark of *Rauwolfia serpentina*, Benth. (300 kg.), was extracted with methanol and on removal of the solvent *in vacuo* gave a brown-yellow, viscous residue (30 kg.). This was mixed with " Hyflo " * (20 kg.) and repeatedly triturated with water (total, 380 l.). The easily separated aqueous extract (*ca.* 300 l.) was dark brown and extremely bitter, and gave copious precipitates with reagents, such as Mayer's, for alkaloids. The extract was processed in batches of 20 l. An equal volume of ether, containing 10% of methanol, was added and the pH (glass electrode) adjusted to 7·0. The mixture was stirred for 0·5 hr. and then separated. The ethereal layer contained weak bases: all the ajmaline and certain quaternary bases remained in the aqueous solution. The latter was again mixed with ether (20 l.) containing 10% of methanol, and the pH was adjusted to 9·2 by the addition of ammonia. After being stirred again for 0·5 hr. the layers were separated and the aqueous layer was worked up for serpentine and other bases (cf. Schlittler and Schwarz, *Helv. Chim. Acta*, 1950, **33**, 1463). The filtered ethereal layer was extracted in portions of about 5 l. with 100 c.c. and then 6 × 50 c.c. portions of 2N-hydrochloric acid.

Ajmaline hydrochloride crystallised from the first two or three extracts and the yield was about 0·1% but was not consistent. The salt (30 g.) was purified by dissolution in boiling water (charcoal) (200 c.c.), and about 25 g. were obtained on cooling of the filtered solution. Further small quantities were recovered from mother-liquors.

Ajmaline and its derivatives. Ajmaline recrystallised from methanol, as colourless rods, m. p. 158—160° (previous swelling), pK_a 8·15 (Found: C, 70·4; H, 8·5; N, 8·0; MeO, 8·0; MeN, 7·5; *C*-Me, 4·6, 4·6; active H, 0·91. $C_{20}H_{26}O_2N_2,CH_4O$ requires C, 70·4; H, 8·4; N, 7·8; 1NMe, 8·1; 1*C*-Me, 4·2; 3 active H, 0·84%). After being heated above its m. p. it sometimes crystallised again, or did so on scratching or seeding, to give crystalline anhydrous ajmaline, $[\alpha]_D^{20}$ +144° (*c*, 0·8 in $CHCl_3$), m. p. 205—207° (rapid heating), or 200—202° (slow heating). At about 220° there was almost complete conversion into *iso*ajmaline which usually crystallised, and melted again at 260—263° (decomp.). The crystalline anhydrous ajmaline gave after recrystallisation from methanol a product showing a behaviour identical with that of the original ajmaline.

Ajmaline and all its derivatives (including those of the *iso*ajmaline series), except the hexahydro-compounds and bromoajmaline, exhibit reactions similar to those of strychnidine. With ferric chloride in weakly acid solution a red colour is produced as the result of oxidation; nitric acid gives an immediate red colour. Diazobenzenesulphonic acid couples in acetic acid solution to an orange-yellow dye which is an indicator of methyl-orange type. The base

* A heat-treated siliceous earth (cf. Strain, *J. Biol. Chem.*, 1924, **105**, 123).

produced on reduction with sodium hydrosulphite (dithionite) shows the typical reactions of a *p*-dialkylaminoaniline.

An ethereal solution of dry hydrogen chloride was added to a solution of ajmaline (0·5 g.) in just sufficient anhydrous methanol (6 c.c.) until acid to Congo-red. Dry ether was then added to turbidity and *ajmaline dihydrochloride* soon crystallised in rectangular plates, which were washed with ether. The m. p. of an anhydrous sample was 305—306° (decomp.) (Found, in anhyd. material : C, 59·8; H, 6·9; C, 17·7, 17·6. $C_{20}H_{26}O_2N_2,2HCl$ requires C, 60·1; H, 7·0; Cl, 17·8%).

Attempts to crystallise ajmaline dihydrochloride (m. p. 250°) from water or dilute hydrochloric acid gave aggregates of prisms, m. p. 140° (decomp.). This, the hydrated *monohydrochloride*, was also obtained by boiling ajmaline with dilute hydrochloric acid for a few minutes (Found : loss at 100° *in vacuo*, 8·8. $C_{20}H_{26}O_2N_2,HCl,2H_2O$ requires $2H_2O$, 9·0%) (Found, in anhyd. material : C, 65·8; H, 7·3; Cl, 9·6. $C_{20}H_{26}O_2N_2,HCl$ requires C, 66·2; H, 7·4; Cl, 9·8%).

A solution of methyl iodide (0·5 c.c.) and ajmaline (0·5 g.) in chloroform (2 c.c.) was kept at room temperature for 24 hr. *Ajmaline methiodide*, which gradually separated in the form of prismatic needles, was collected, washed with chloroform, and dried (0·52 g.). The salt crystallised from aqueous methanol in minute prisms, m. p. 229° (decomp.) (anhyd.) (Found, in material dried at 100° *in vacuo* : C, 53·9, 53·7, 53·9; H, 6·2, 6·2, 6·4; I, 26·7, 26·8. $C_{21}H_{29}O_2N_2I$ requires C, 53·9; H, 6·2; I, 27·1%). This substance did not titrate as a true quaternary salt, but as the salt of a base of pK_a 9·2 (0·03M in H_2O). It gave a negative reaction with *m*-dinitrobenzene and methanolic potassium hydroxide.

A solution of ajmaline methiodide (0·4 g.) in water (8 c.c.) was digested with an excess of freshly prepared silver chloride for 2 hr., then filtered and concentrated to a syrup, which deposited needles *in vacuo* over sulphuric acid. After contact with porous porcelain the colourless mass (0·2 g.) was crystallised from a few drops of water and dried over sulphuric acid; it had m. p. 215° if air-dried. The sulphuric acid-dried *methochloride*, crystallised from methanol–ether, had m. p. 288—290° (decomp.) (Found in material dried at 100° *in vacuo* : Cl, 9·6. $C_{21}H_{29}O_2N_2Cl$ requires Cl, 9·4%). The methochloride gives the characteristic colour tests for ajmaline, *e.g.*, with diazotised sulphanilic acid it gives a methyl-orange type of azo-compound.

Ajmaline methiodide (0·3 g.), dissolved in water, was treated while hot with dilute aqueous ammonia, and the solution was extracted with chloroform. The heavy viscous oil which remained after removal of the solvent solidified on trituration with absolute methanol. It (0·17 g.) crystallised from aqueous ethanol in rectangular plates, m. p. 124° (Found, in material dried at 100° *in vacuo* : C, 70·6; H, 8·4. $C_{21}H_{30}O_3N_2$ requires C, 70·4; H, 8·4%). This *methohydroxide* (or tautomer) is readily soluble in water, alcohol, or chloroform, less readily so in ether. The substance was distilled at 0·01 mm., a colourless hygroscopic glass being obtained (Found : C, 73·45; H, 9·0. $C_{21}H_{28}O_2N_2$ requires C, 74·1; H, 8·3%). This proved to be N-*methyl*iso*ajmaline*, readily soluble in water to give an alkaline solution. On neutralisation with dilute hydrochloric acid and addition of potassium iodide, a gum was obtained which after two crystallisations from water afforded colourless prisms, m. p. 195° (ajmaline methiodide, similarly recrystallised, had m. p. 129—131°) alone or mixed with *iso*ajmaline methiodide of m. p. 195—196°.

Attempted Condensation of Ajmaline and Ethanedithiol.—A solution of ajmaline (0·2 g.) in glacial acetic acid (5 c.c.) containing ethanedithiol (0·5 g.) was saturated with dry hydrogen chloride at 0° and then kept for 24 hr. at the room temperature. The clear orange solution was diluted with water, made alkaline with 10% sodium hydroxide solution, and then extracted with ether. The ethereal solution was shaken with 2% hydrochloric acid, and the acid solution made alkaline with ammonia and again extracted with ether. Evaporation of the solvent and crystallisation from aqueous methanol gave unchanged ajmaline, m. p. and mixed m. p. 158—160°.

A similar experiment with *iso*ajmaline yielded unchanged *iso*ajmaline, m. p. and mixed m. p. 260—265°.

Bromoajmaline.—A solution of ajmaline (0·34 g.) in dry chloroform (4 c.c.) was treated dropwise and with efficient ice-cooling with a solution of bromine (0·17 g.) in dry chloroform (10 c.c.) until the colour of bromine was permanent. Crystalline *bromoajmaline hydrobromide* gradually separated. Next day, this was collected, washed with dry ether, and dried (yield 0·3 g.). It crystallised from alcohol in plates or from water in prisms, the m. p. of anhydrous material being 295° (decomp.) (Found, in material dried at 120° *in vacuo* : C, 49·2; H, 5·3; Br, 33·4. $C_{20}H_{25}O_2N_2Br,HBr$ requires C, 49·4; H, 5·4; Br, 32·9%). A solution of the compound in distilled water gave a precipitate of silver bromide on addition of silver nitrate.

A solution of the hydrobromide (0·25 g.) in hot water (5 c.c.) was basified with dilute aqueous ammonia. The dense white precipitate of the *bromo*-base was washed with water and dried (0·11 g.). It crystallised from aqueous methanol in microscopic needles, m. p. 182° (decomp.) (Found, in material dried at 100° *in vacuo*: C, 59·1; H, 6·1; Br, 19·3. $C_{20}H_{25}O_2N_2Br$ requires C, 59·3; H, 6·2; Br, 19·7%). Neither the bromo-hydrobromide nor the free bromo-base exhibited any of the colour reactions of ajmaline.

Diacetylajmaline.—Ajmaline (0·4 g.), dissolved in the minimum of boiling benzene (4 c.c.), was refluxed with acetic anhydride (4 c.c.) for 6 hr. The benzene and excess of anhydride were removed as completely as possible under reduced pressure, and the residue was taken up in water and made alkaline with dilute ammonia. The acetyl compound, which separated as a voluminous white mass, was taken up in ether. On evaporation of the solvent, a heavy viscous oil remained which solidified on trituration with a mixture of ether and light petroleum (b. p. 40—60°). The solid was collected and washed with light petroleum. It crystallised from ether–light petroleum (b. p. 40—60°) in minute prisms, or from aqueous alcohol in prismatic needles, m. p. of anhydrous sample 132° (Found, in material dried at 100° *in vacuo*: C, 70·2, 70·2; H, 7·4, 7·3; AcO, 22·5. $C_{24}H_{30}O_4N_2$ requires C, 70·2; H, 7·3; 2AcO, 21·0%). The *acetyl* compound is very readily soluble in the usual organic solvents, responds to the colour tests for ajmaline, and is easily soluble in dilute acids. After some years the matter was reinvestigated and a more stable polymorph was then isolated.

Ajmaline (2 g.) was refluxed with benzene (25 c.c.) and acetic anhydride (10 c.c.) for 12 hr., then evaporated *in vacuo* to dryness and the residue taken up in a little ether. Careful addition of light petroleum (b. p. 40—60°) caused the separation of thick, colourless rods (1·27 g.), m. p. 187—189°. Sometimes a metastable form crystallised, m. p. 130—132° (with resolidification and then m. p. 187—189°), but this readily changed to the higher-melting form (Found: C, 70·2; H, 7·4; N, 7·1. $C_{24}H_{30}O_4N_2$ requires C, 70·2; H, 7·4; N, 6·8%). $[\alpha]_D$ was +16° (*c* 2·7 in $CHCl_3$), and pK_a 4·9. It dissolved readily in dilute acid, but it gave a neutral solution in aqueous alcohol.

Attempts to oxidise this compound with potassium permanganate in acetone gave mainly unchanged product; on prolonged treatment only a trace of a substance giving a violet Otto reaction was obtained.

Hydrolysis of Diacetylajmaline.—(*a*) Diacetylajmaline (0·1 g.) was refluxed with 0·1N-hydrochloric acid for 2 hr. in a stream of nitrogen. The solution was basified and extracted with ether. The ether was evaporated, leaving a colourless residue which when crystallised from a little methanol had m. p. 158—160°, undepressed by ajmaline.

(*b*) Diacetylajmaline (0·03 g.), dissolved in dry ether (10 c.c.), was added to an ethereal solution of lithium aluminium hydride (15 c.c. of 1%). After 5 hr. the mixture was carefully decomposed at 0° with water, and after addition of 5% potassium hydroxide (2 c.c.) the ethereal layer was decanted. The crystalline residue obtained on evaporation was recrystallised from aqueous methanol and had m. p. 154—156°, undepressed by ajmaline (yield 0·02 g.). The hydrochloride, crystallised from water, had m. p. 132—133°.

(*c*) Diacetylajmaline (0·05 g.) was dissolved in methanol (1 c.c.) containing potassium hydroxide (0·01 g.). The mixture was refluxed for 15 min. and then diluted with water, giving colourless crystals (0·03 g.), m. p. 158—160°, undepressed by ajmaline.

Diacetylajmaline Methiodide.—A solution of diacetylajmaline in methyl iodide was kept for 1 hr. It was then evaporated to dryness and the residue crystallised from water. Clusters of colourless prisms, m. p. 251—253° (decomp.), were obtained (Found, in material dried at 100° *in vacuo* over P_2O_5: C, 54·3; H, 5·7; N, 4·8; I, 23·4. $C_{25}H_{33}O_4N_2I$ requires C, 54·4; H, 6·0; N, 5·1; I, 23·0%). The aqueous solution gave no precipitate with ammonia.

Benzoylajmaline.—Ajmaline (0·4 g.), dissolved in just sufficient dry benzene (4 c.c.), was refluxed with freshly distilled benzoyl chloride (0·8 c.c.) for 30 min. The hydrochloride of the benzoylated base very soon separated as a chalky powder, which was collected and washed repeatedly with dry ether and benzene. Very thorough washing is necessary in order to remove the last traces of benzoyl chloride, the presence of which hinders the subsequent purification by crystallisation. The *hydrochloride* (0·34 g.) crystallised from anhydrous methanol–ether in small needles, m. p. 267° (decomp.) (Found, in material dried at 120° *in vacuo*: C, 69·4, 69·3; H, 6·5, 6·5. $C_{27}H_{30}O_3N_2$,HCl requires C, 69·4; H, 6·5%). Like ajmaline hydrochloride, benzoylajmaline hydrochloride is insoluble in cold, but readily soluble in hot, water.

A solution of benzoylajmaline hydrochloride (0·4 g.) in just sufficient hot water was made alkaline with dilute ammonia. The thick white precipitate which separated was taken up in ether. On evaporation of the solvent an amorphous powder remained which crystallised from

ether in colourless, microscopic needles, or from aqueous methanol in prisms (yield 0·2 g.), m. p. of anhydrous material, 219° (Found, in material dried at 100° *in vacuo* : C, 74·9, 74·9; H, 7·0, 7·1. Calc. for $C_{27}H_{30}O_3N_2$: C, 75·3; H, 7·0%). Benzoylajmaline is soluble in dilute acids with difficulty.*

A solution of benzoylajmaline (0·2 g.) in anhydrous methanol (2 c.c.) was mixed with an ethereal solution of dry hydrogen chloride and further diluted with a little dry ether until just turbid. The *dihydrochloride* soon separated in minute needles, which, washed with dry ether and dried (0·11 g.), had m. p. 244—245° (decomp.) (Found, in material dried at 120° *in vacuo* : Cl, 14·5. $C_{27}H_{30}O_3N_2,2HCl$ requires Cl, 14·1%). This is very readily soluble in water.

Ajmaline Oxime.—Ajmaline (0·5 g.) was boiled for 10—15 min. with a solution of hydroxylamine hydrochloride (0·5 g.) in water (5 c.c.), then kept in the cold for 2—3 hr. *Ajmaline oxime hydrochloride* which separated (yield 0·25 g.) crystallised from water in colourless needles, m. p. (anhyd.) 218° (effervescence) (Found : loss at 100°, 4·1. $C_{20}H_{27}O_2N_3,HCl,2H_2O$ requires $1H_2O$, 4·3. Found, in dried material : C, 60·4; H, 7·5; N, 10·4. $C_{20}H_{27}O_2N_3,HCl,H_2O$ requires C, 60·6; H, 7·6; N, 10·6%).

A solution of this hydrochloride (0·2 g.) in water (4 c.c.) was basified with ammonia, the free *oxime* being precipitated (yield 0·14 g.). It crystallised from methanol in minute prisms, m. p. 220° (Found, in material dried at 100° *in vacuo* : C, 70·6; H, 7·8; N, 12·1. $C_{20}H_{27}O_2N_3$ requires C, 70·4; H, 7·9; N, 12·3%).

Anhydroajmaline Oxime.—Ajmaline oxime hydrochloride (0·67 g.) was suspended in a mixture of acetic acid (5 c.c.) and acetic anhydride (2 c.c.), and dry hydrogen chloride led in without cooling. All the solid went into the solution. When the mixture was kept at the room temperature for 3 hr. colourless needles separated. After cooling in ice the product was collected and dried at 100° (0·76 g.). Recrystallised from glacial acetic acid containing a little hydrogen chloride it had m. p. 202—205°, with previous sintering at 198—200° (Found, after drying at 100° *in vacuo* over P_2O_5 : C, 57·1; H, 6·7; N, 8·6; Cl, 14·3; AcO, 18·2. $C_{24}H_{33}O_4N_3Cl_2$ requires C, 57·8; H, 6·7; N, 8·4; Cl, 14·2; 2AcO, 17·2%). This substance has the composition of a *diacetylajmaline oxime dihydrochloride*. It was dissolved in methanol (20 c.c.) and treated with methanolic potassium hydroxide until alkaline. The solution was refluxed for 4 min. and then diluted with water (80 c.c.). Colourless needles of *anhydroajmaline oxime* separated (0·44 g.), having m. p. 254—255° unchanged by recrystallisation from aqueous methanol, $[\alpha]_D^{17\cdot5}$ +29° (*c*, 1·4 in $CHCl_3$) (Found : C, 74·2; H, 7·7; N, 12·8; *C*-Me, 4·95; active H, 0·44. $C_{20}H_{25}ON_3$ requires C, 74·4; H, 7·8; N, 13·0; *C*-Me, 4·65; 2H, 0·6%).

Anhydro-N-methylajmaline Oxime Hydriodide.—Anhydroajmaline oxime (0·110 g.) was refluxed with methyl iodide (2 c.c.) in acetone (5 c.c.) containing anhydrous potassium carbonate (1 g.) for 2 hr. The solution was filtered, the residue was washed with hot acetone, and the combined filtrates were evaporated to a small bulk and diluted with water. Boiling and scratching caused crystallisation. Recrystallisation from water with the addition of potassium iodide yielded the *N-methyl hydriodide* as colourless, elongated plates, m. p. 279—280°, with sintering at 275° (Found, in material dried at 100° *in vacuo* : C, 54·5; H, 6·2; N, 8·9; I, 26·8. $C_{21}H_{27}ON_3,HI$ requires C, 54·2; H, 6·1; N, 9·0; I, 27·3%). Its aqueous solution gave an immediate precipitate with dilute ammonia, which did not dissolve even on boiling.

Hydrolysis of Anhydroajmaline Oxime.—Anhydroajmaline oxime (0·2 g.) was refluxed with 25% hydrochloric acid (4 c.c.) for 6 hr., then cooled in ice. Colourless prisms were slowly deposited. The product was collected and recrystallised from methanol–ether, colourless needles of *dihydrochloride* being obtained (0·15 g.), which sintered at 150° and softened and reddened above 250° but were not completely liquid until 275° (Found, in material dried at 100° *in vacuo* over P_2O_5 : C, 57·8; H, 6·8; N, 6·9. $C_{20}H_{26}O_3N_2,2HCl$ requires C, 57·8; H, 6·8; N, 6·7%). The substance lost no weight at 140° *in vacuo*. The aqueous mother-liquor from the hydrolysis evolved ammonia when warmed with sodium hydroxide. This dihydrochloride was very soluble in water and could not be extracted from the solution by chloroform in either neutral or alkaline solution. It did not have any tendency to lactamise or lactonise in acid or neutral solution.

The free amino-acid has not been isolated. The constitution of anhydroajmaline oxime is discussed in the introductory section.

Reduction of Anhydroajmaline Oxime with Lithium Aluminium Hydride.—Anhydroajmaline oxime (0·05 g.) was dissolved in chloroform (2 c.c.) and added to lithium aluminium hydride (0·05 g.) in ether (20 c.c.). The mixture was set aside at room temperature for 2 hr., then

* Dr. H. MacPhillamy has now prepared dibenzoylajmaline by treatment of the base with benzoyl chloride in cold pyridine. An account of this experiment will be submitted in Part II.

decomposed with water; dilute hydrochloric acid (5 c.c.) was added, and the solution warmed on a steam-bath for 10 min. After addition of potassium hydroxide the solution was extracted with chloroform. The extract was evaporated to dryness and the residue triturated with a little methanol; it crystallised, and had m. p. 154—158°, undepressed when mixed with ajmaline.

Action of Sulphurous Acid on Ajmaline.—On gentle warming of a suspension of ajmaline (0·2 g.) in saturated aqueous sulphur dioxide (8 c.c.) the colour changed to pale yellow and a crystalline precipitate separated. The mixture was mechanically stirred for 2 hr. The precipitated *product* was then collected, washed with cold water, and dried (0·2 g.). It was rather sparingly soluble in hot water but easily soluble in hot methanol and crystallised from a concentrated solution in methanol, with the addition of a drop of hot water, in shining colourless plates, m. p. 225° (when heated moderately quickly) (Found: C, 57·4; H, 7·1; S, 7·1, 7·2; loss at 100° *in vacuo*, 22·9. $C_{20}H_{26}O_2N_2,H_2SO_3,H_2O$ requires C, 57·6; H, 7·0; S, 7·5; H_2SO_3,H_2O, 23·4%).

iso*Ajmaline.*—(*a*) Ajmaline (1 g.) was added to a solution of potassium hydroxide (1 g.) in methanol (50 c.c.), and the mixture refluxed on the steam-bath for 6 hr. About three-fourths of the methanol were removed by distillation and the warm solution was diluted with water, a heavy viscous oil separating. This was again brought into solution by warming on the steam-bath and adding a few drops of methanol; on cooling, *iso*ajmaline gradually separated as an amorphous powder which was collected, washed with water, and dried (0·85 g.). It crystallised from aqueous methanol in minute prisms or from ether in plates, m. p. 265° (decomp.) (Found, in material dried at 100° *in vacuo*: C, 73·5, 73·6, 7·35; H, 7·9, 7·9, 8·0; N, 8·3. Calc. for $C_{20}H_{26}O_2N_2$: C, 73·6; H, 8·0; N, 8·6%). The conversion was incomplete in less than 6 hr.; methanol could be replaced by ethanol without affecting the results.

(*b*) Ajmaline (0·2 g.) was heated at 200—220°/12 mm. for 4—5 hr. It sublimed in beautiful glistening plates. If, however, the temperature was raised above 250° a resinous mass distilled together with a small crystalline sublimate. The whole (0·1 g.) was washed with a little ether. It crystallised from dilute methanol in minute prisms, m. p. 265° alone or mixed with the previous specimen of *iso*ajmaline (Found: C, 73·4, 73·5; H, 8·0, 7·9. Calc. for $C_{20}H_{26}O_2N_2$: C, 73·6; H, 8·0%).

iso*Ajmaline*, recrystallised from aqueous alcohol and dried *in vacuo* over P_2O_5 (Found: C, 73·9; H, 8·2; N, 8·5; *C*-Me, 5·7, 5·0, 4·9; active H, 0·61, 0·61. $C_{20}H_{26}O_2N_2$ requires C, 73·6; H, 8·1; N, 8·6; *C*-Me, 4·6; 2H, 0·62%), had $[\alpha]_D^{18}$ +72° (*c* 0·7 in $CHCl_3$) and pK_a 8·05.

iso*Ajmaline Derivatives.*—*iso*Ajmaline (0·1 g.), dissolved in the minimum quantity of hot methanol, was treated with ethereal hydrogen chloride until just turbid, then kept for some time in the cold. iso*Ajmaline dihydrochloride* crystallised in glistening plates, m. p. 254° (decomp.) (air-dried), m. p. 310° (decomp.) (anhyd.) (Found, in material dried at 120° *in vacuo*: C, 59·9; H, 6·9; Cl, 18·1. $C_{20}H_{26}O_2N_2,2HCl$ requires C, 60·1; H, 7·0; Cl, 17·8%). Siddiqui and Siddiqui (*loc. cit.*) gave m. p. 238—249° (decomp. with previous frothing) for the amorphous dihydrochloride. The hydrochloride was recovered unchanged even on prolonged boiling with anhydrous methanol.

The dihydrochloride, m. p. 254°, on crystallisation from water gave a salt, m. p. 147° (decomp.). The same *hydrochloride*, m. p. 147°, was also obtained by boiling *iso*ajmaline with dilute hydrochloric acid. It crystallised from water in prisms, m. p. 147° (anhyd.) (Found: loss at 100° *in vacuo*, 8·7. $C_{20}H_{26}O_2N_2,HCl,2H_2O$ requires $2H_2O$, 9·0%). *iso*Ajmaline hydrochloride, like ajmaline hydrochloride, is very sparingly soluble in cold water. iso*Ajmaline picrate* was prepared by adding an ethereal solution of picric acid to a solution of the base in anhydrous methanol; it crystallised from alcohol as small yellow needles, m. p. 225° (decomp.) with previous frothing (Found, in material dried at 100° *in vacuo*: C, 56·0; H, 5·1; N, 12·3. $C_{26}H_{29}O_9N_5$ requires C, 56·2; H, 5·2; N, 12·6%).

*iso*Ajmaline (0·4 g.), dissolved in chloroform, was treated with excess of methyl iodide and left at the room temperature for 48 hr. A heavy oil gradually separated. This was collected, washed with chloroform, and then digested with methanol–ether, whereupon it solidified. The solid *methiodide* was dissolved in methanol and precipitated with dry ether. After repetition of this process, the material (0·22 g.) was crystallised from acetone–ether. It afforded minute, pale yellow prisms, which darkened at 185° and had m. p. 200—203° (Found, in material dried at 100° *in vacuo*: C, 53·5; H, 6·2; I, 26·8. $C_{21}H_{29}O_2N_2I$ requires C, 53·9; H, 6·2; I, 27·1%). *iso*Ajmaline methiodide, m. p. 194—195° (from acetone), behaved on titration with 0·1N-sodium hydroxide as the salt of a base of pK_a 9·4. It gave no colour when warmed with pure *m*-dinitrobenzene in aqueous-methanolic potassium hydroxide.

A solution of the methiodide (0·3 g.) in hot water was treated with ammonia and allowed to cool. No solid separated even on long keeping. The solution was extracted with chloroform, and the extract washed with water and dried (Na_2SO_4). After removal of the solvent, a heavy viscous oily *methohydroxide* remained which solidified on trituration with absolute ethanol (yield, 0·16 g.). It crystallised from aqueous alcohol in plates, which softened, with evolution of gas, at 119°, had m. p. 121° (Found, in material dried at 100° *in vacuo*: C, 70·2; H, 8·3. $C_{21}H_{30}O_3N_2$ requires C, 70·4; H, 8·4%), and were readily soluble in water, alcohol, and methanol, less so in ethyl acetate, and difficultly so in ether.

iso*Ajmaline Oxime*.—*iso*Ajmaline (0·3 g.) was refluxed for 20 min. with a solution of hydroxylamine hydrochloride (0·3 g.) in water (3 c.c.). The oxime hydrochloride did not separate even at 0°. Addition of ammonia precipitated the *oxime* (0·2 g.) which crystallised from methanol as prisms, m. p. (anhyd.) 185° (Found, in material dried at 100° *in vacuo*: C, 70·3; H, 7·8; N, 12·2. $C_{20}H_{27}O_2N_3$ requires C, 70·4; H, 7·9; N, 12·3%).

*Diacetyliso*ajmaline.—*iso*Ajmaline (0·3 g.) was suspended in dry benzene (5 c.c.) and refluxed with freshly distilled acetic anhydride (4 c.c.) for 5 hr. The excess of anhydride and benzene were removed as completely as possible. The residue was taken up in water and made alkaline with ammonia. The precipitate was extracted with ether, washed with water, and dried (Na_2SO_4). After removal of the solvent a crystalline *diacetyl* derivative (0·13 g.) remained, which crystallised from ether in thin plates, m. p. (anhyd.) 224—225° (Found, in material dried at 100° *in vacuo*: C, 70·0; H, 7·4; AcO, 21·9. $C_{24}H_{30}O_4N_2$ requires C, 70·3; H, 7·3; 2AcO, 21·0%). On titration the pK_a was found to be *ca.* 3·8.

*Benzoyliso*ajmaline *Hydrochloride*.—This was prepared from *iso*ajmaline as described for benzoylajmaline. The *hydrochloride* (0·13 g.), crystallised from anhydrous methanol–ether, had m. p. 258° (decomp.) (anhyd.) (Found, in material dried at 120° *in vacuo*: C, 69·2; H, 6·6; Cl, 7·9. $C_{27}H_{30}O_3N_2$,HCl requires C, 69·4; H, 6·6; Cl, 7·6%). It is more readily soluble in water than *iso*ajmaline hydrochloride.

Benzoyl*iso*ajmaline was prepared from the hydrochloride in the usual way and was obtained as an amorphous white powder, m. p. 195° with frothing from 186°, which could not be induced to crystallise.

*Bromoiso*ajmaline.—A solution of *iso*ajmaline (0·34 g.) in dry chloroform (4 c.c.) was treated drop-wise with a solution of bromine (0·2 g.) in dry chloroform (10 c.c.) with efficient ice-cooling, till the colour of bromine was permanent (bromine consumed, 0·17 g., *ca.* 1 mol.). A crystalline precipitate separated. The mixture was kept in the ice-chest and next day the *bromo-hydrobromide* was collected, washed with dry ether, and dried (0·29 g.). It crystallised from water in prisms, m. p. (anhyd.) 288—289° (decomp.) (Found, in material dried at 120° *in vacuo*: C, 49·2; H, 5·4; Br, 33·4. $C_{21}H_{25}O_2N_2Br$,HBr requires C, 49·4; H, 5·4; Br, 32·9%), and was insoluble in cold water but readily dissolved in boiling water. It does not respond to any of the colour tests for *iso*ajmaline.

A solution of this hydrobromide (0·2 g.) in hot water (5 c.c.) was basified with dilute ammonia. The dense white precipitate of the *bromo*-base (0·12 g.) which separated was collected, washed with water, and dried. It crystallised from aqueous methanol in minute needles, m. p. (anhyd.) 192° (decomp.) (Found, in material dried at 100° *in vacuo*: C, 59·2; H, 6·2; Br, 19·9. $C_{20}H_{25}O_2N_2Br$ requires C, 59·3; H, 6·2; Br, 19·8%).

*Cleavage of Diacetyliso*ajmaline *with Lithium Aluminium Hydride*.—Diacetyl*iso*ajmaline (0·04 g.) in anhydrous ether (15 c.c.) was added to a solution of lithium aluminium hydride (0·04 g.) in ether (15 c.c.). After 4 hr. the excess of reagent was decomposed with ethyl acetate, and then water (10 c.c.) and 10% sodium hydroxide solution (5 c.c.) were added. The ethereal layer gave, after evaporation of the solvent, a colourless residue which readily crystallised from aqueous alcohol, m. p. 260—262° with previous sintering at 250°, mixed m. p. with *iso*ajmaline, 260—262°.

*Anhydroiso*ajmaline *Oxime*.—A solution of *iso*ajmaline oxime (0·5 g.) in acetic acid (5 c.c.) and acetic anhydride (2 c.c.) was saturated with hydrogen chloride. After a day the mixture was evaporated to dryness *in vacuo* and the residue dissolved in methanol (10 c.c.). 5% Methanolic potassium hydroxide was added until the solution was alkaline, the mixture was then refluxed for 2 min., and more alkali was added to keep the solution alkaline. Dilution with water (100 c.c.) caused the separation of *anhydroisoajmaline oxime* (0·3 g.), m. p. 218—220°. Recrystallisation from aqueous methanol gave long needles, m. p. 219—220°, $[\alpha]_D^{19}$ +74° (*c*, 1·2 in chloroform) (Found: C, 74·2; H, 7·6. $C_{20}H_{25}ON_3$ requires C, 74·4; H, 7·8%).

Reduction of Anhydroisoajmaline Oxime with Lithium Aluminium Hydride.—Anhydro*iso*ajmaline oxime (0·05 g.) was dissolved in chloroform (2 c.c.) and added to a solution of lithium

aluminium hydride (0·05 g.) in ether (20 c.c.). The solution was kept at room temperature for 2 hr. and then decomposed with water and dilute hydrochloric acid (5 c.c.). The mixture was heated on a steam-bath for 10 min., cooled, made alkaline with potassium hydroxide, and extracted with chloroform. Evaporation of the solvent left a colourless glass which when moistened with methanol crystallised; several recrystallisations raised the melting point to 260—262° undepressed by admixture with *iso*ajmaline.

Some Negative Results.—*iso*Ajmaline was recovered from attempts to condense it with salicylaldehyde or piperonaldehyde in the presence of basic catalysts. Neither ajmaline nor *iso*ajmaline could be reduced by lithium aluminium hydride in tetrahydrofuran or dioxan solution. Ajmaline was not reduced by zinc and boiling dilute hydrochloric acid.

Experiments on the Degradation of Ajmaline.—(I) Ajmaline (1 g.), intimately mixed with soda-lime (15 g.), was gradually heated in a metal-bath in a slow current of nitrogen until the temperature rose to 220° (after about ½ hr.). At this temperature, a liquid began to distil. The temperature was kept at 280—300° for 10—12 hr., after which no more liquid distilled. As a result or many trials it was found that the yield of the distillate depended mainly on the following factors: (i) In no case should the temperature be raised above 300° as otherwise no distillate could be obtained. (ii) The temperature must be raised slowly at a uniform rate. (iii) The quality of the soda-lime had a marked influence on the yield of the base. The soda-lime should be dried over phosphoric anhydride *in vacuo*.

The residue in the flask was exhaustively extracted with ether and the extract was added to the ethereal solution of the distillate. The combined ethereal extracts were washed with dilute hydrochloric acid, the yellow hydrochloride which separated being brought into solution by the addition of a few c.c. more of dilute hydrochloric acid. For the treatment of the acid washings (C) see below. The extract was washed with dilute alkali, then with water, and dried. The solvent was removed by evaporation and the residue distilled at low pressure, giving (A), b. p. 120—125°/0·2 mm. (bath-temp.), and a larger fraction (B), b. p. 190—200°/0·2 mm. (bath temp.).

The fraction (A) gave a positive pine-shaving test. With Ehrlich's reagent it gave a strong bluish-purple colour similar to that given by β-substituted indole derivatives. Fraction (B) gave reactions suggestive of the presence of carbazole, namely, a positive pine-shaving test but no response to Ehrlich's reagent, and a golden-yellow colour in concentrated sulphuric acid, changed to bluish-green on the addition of a trace of concentrated nitric acid (Blom, *Helv. Chim. Acta*, 1921, **4**, 625). Furthermore, when warmed with acetaldehyde or formaldehyde in the presence of concentrated sulphuric acid the oil (B) gave a deep blue colour (Dische, *Biochem. Z.*, 1927, **189**, 77). Further, the ultra-violet absorption spectrum of this fraction showed all the characteristic bands for carbazole. All attempts to induce the oil to crystallise, however, were unsuccessful.

The yellow acid washings (C) were boiled with animal charcoal and the filtered solution concentrated to a small bulk on the steam-bath. The crystalline *hydrochloride* which separated on cooling was collected and, recrystallised from dilute hydrochloric acid, had m. p. (anhyd.) 282° (decomp.) (yield, 0·32 g.) (Found, in material dried at 120° *in vacuo*: C, 66·9; H, 5·5; Cl, 15·4. $C_{13}H_{12}N_2$,HCl requires C, 67·1; H, 5·6; Cl, 15·3%).

The pure hydrochloride (0·3 g.) was dissolved in the minimum quantity of water and the solution made alkaline with concentrated aqueous sodium hydroxide; the precipitated base was extracted with a large volume of ether in which it was somewhat sparingly soluble. The ethereal extract was washed with water and dried (K_2CO_3). On removal of the solvent, the residual oil was triturated with light petroleum (b. p. 40—60°); it then solidified and was purified by sublimation in a high vacuum. It then separated from ether in glistening needles (0·1 g.), m. p. (anhyd.) 102° (Found, in material dried at 80° *in vacuo*: NMe, 10·7; *C*-Me, 7·2. $C_{13}H_{12}N_2$ requires NMe, 14·8; *C*-Me, 7·6%). The base, ind-N-*methylharman*, was readily soluble in the usual organic solvents, less readily in ether.

(II) An intimate mixture of ajmaline (3 g.) and zinc dust (32 g.), covered with a layer of zinc dust, was heated in a hard-glass tube at 380—400°. The tube was heated in a metal-bath, the temperature of which was recorded by a thermocouple. Hydrogen was passed through the tube for 10—15 min. before the heating, and the temperature was raised slowly and uniformly. When the temperature reached approx. 380°, volatile material was copiously evolved and immediately afterwards a liquid began to distil. The products of the distillation were led through a side-tube to a long tube, provided with a water-jacket, in which most of the liquid condensed. The end of this tube was connected to a series of bubblers, the first containing water, the second N-hydrochloric acid, and the third N-potassium hydroxide. The heating was

continued for 10—12 hr., after which no further liquid distilled. The tube was then allowed to cool slowly to room temperature and the residue in it was repeatedly digested with ether. The extract was added to an ethereal solution of the distillate. The combined ethereal solutions (A) were washed with N-hydrochloric acid, which became yellow (washing with hydrochloric acid was continued until the washings were colourless), and then with N-potassium hydroxide. For treatments of the acid-washings (B) and alkali-washings (C) see below.

The ethereal solution (A) was washed with water (until the washings were neutral), dried (Na_2SO_4), and filtered. The solvent was then removed and the residual oil was distilled, giving fractions, (*a*) b. p. 80—90°/0·2 mm., (*b*) b. p. 110—120°/0·2 mm., and (*c*) b. p. 180—200°/0·2 mm. (all bath-temps.). The first two fractions, which were very small, were distilled from small bulbs. The distillate from the first two fractions showed a positive pine-shaving test and with Ehrlich's reagent gave a deep bluish-purple colour similar to that given by β-substituted indole derivatives. Solutions of the oils in organic solvents exhibited a dull, blue fluorescence in ultra-violet light, characteristic of some indole derivatives.

The fraction (*c*) was distilled at $4·9 \times 10^{-3}$ mm., giving two fractions (*d*) and (*e*). Only one or two drops of (*d*) were obtained boiling at 120—125° (bath-temp.). The rest of the liquid boiled at 140—150° (bath-temp.) and the oil gave a positive pine-shaving test but did not colour with Ehrlich's reagents; it also gave the characteristic colour tests for carbazole (Blom, Dische, *locc. cit.*). The oil, dissolved in light petroleum (b. p. 40—60°), was passed through a column of alumina. The solution then had a bluish fluorescence in ultra-violet light whereas carbazole itself has a strong violet fluorescence. On repeated chromatographic separation (seven columns) the impurity which imparted the bluish tinge to the fluorescence was held on the column and the characteristic violet fluorescence of carbazole appeared. Several fractions were collected and evaporated. The first two yielded heavy oils which showed the characteristic colour tests for carbazole. From the third and subsequent fractions solids were obtained. The solid residues from different fractions were combined and, crystallised from light petroleum (b. p. 40—60°), had m. p. 236°. By a mixed m. p. determination and a careful comparison of colour tests and absorption spectra the crystalline product (4 mg.) was found to be carbazole.

The acid-washings (B) were concentrated on the steam-bath to about 30 c.c. and boiled with animal charcoal. The filtered solution was basified with concentrated aqueous sodium hydroxide; the base was precipitated as a semi-solid viscous mass which was taken up by means of ether. After evaporation of the solvent the residual oil was distilled, b. p. 160—165°/0·2 mm. (bath-temp.). The distillate was dissolved in a little ether and treated with N-hydrochloric acid; a yellow hydrochloride which separated crystallised from dilute hydrochloric acid in pale yellow, silky needles, m. p. 282° (decomp.) (yield, 4·0 mg.). The solution in dilute hydrochloric acid had a strong violet fluorescence. The hydrochloride (4 mg.), dissolved in the minimum of water, was made alkaline with concentrated aqueous sodium hydroxide, and the precipitated base was taken up in ether. After evaporation the solid residue crystallised from aqueous methanol in glistening needles (3 mg.), m. p. (anhyd.) 102°. This base was identical with that obtained in the soda-lime distillation (mixed m. p. and ultra-violet absorption).

ind-N-*Methylharman*.—The harman that was required was prepared by the method of Kermack, Perkin, and Robinson (*J.*, 1921, **119**, 1617) from tryptophan (1 g.) (yield, 0·22 g.). The product melted at 237° after one crystallisation from aqueous methanol; it was dried *in vacuo* at 100° before use.

Potassium (0·14 g.) was dissolved in liquid ammonia (10 c.c.) in presence of a trace of ferric nitrate. Harman (0·65 g.) was then added; it very readily passed into solution imparting a dull fluorescence to the liquid. In a short time a yellow precipitate separated. The excess of ammonia was removed by cautious addition of ether and occasional shaking. When nearly all the ammonia had evaporated, the solution was gently warmed for ½ hr.; it was cooled at 18° and methyl iodide (0·24 c.c.), diluted with a large volume of ether, was slowly added. The mixture was slowly heated to 40° and kept at this temperature for 3 hr. The ethereal solution was carefully decanted and the residue in the flask exhaustively extracted with dry ether. The combined ethereal solutions were filtered and evaporated. The residue crystallised from ether in long silky needles or from acetone in plates, m. p. (air-dried) 95°, (anhyd.) 102° (yield, 0·59 g.) (Found, in material dried at 80° *in vacuo*: C, 79·4; H, 6·1; NMe, 12·1; *C*-Me, 7·6. Calc. for $C_{13}H_{12}N_2$: C, 79·6; H, 6·1; NMe, 14·8; *C*-Me, 7·6%). Späth and Lederer (*Ber.*, 1930, **63**, 2102) gave m. p. 102—103°.

The identity of the degradation product from ajmaline with *ind-N*-methylharman was

established by a careful comparison of properties including ultra-violet spectra, m. p., and mixed m. p.

The *hydrochloride* crystallised from dilute hydrochloric acid in long silky needles, m. p. 282° (Found, in material dried at 120° *in vacuo*: C, 66·8; H, 5·5; Cl, 15·1. $C_{13}H_{12}N_2$,HCl requires C, 67·1; H, 5·6; Cl, 15·3%).

ind-*N*-*Methylharmine*.—Treatment of a solution of potassium (0·12 g.) in liquid ammonia (10 c.c.) with harmine (0·65 g.) (see above) gave a solution with a deep violet fluorescence. A yellow precipitate soon separated. Removal of ammonia and treatment with methyl iodide (0·19 c.c.), etc., as above gave a viscous oil which solidified on trituration with acetone. The *ind*-*N*-methylharmine crystallised from acetone in glistening plates and after two recrystallisations had m. p. 117—118° (air-dried), 124—125° (dried over P_2O_5) (yield, 0·42 g.) (Found, in material dried at 80° *in vacuo*: C, 74·1; H, 6·2; N, 12·6; *N*-Me, 10·5; OMe, 11·4. Calc. for $C_{14}H_{14}ON_2$: C, 74·3; H, 6·2; N, 12·4; *N*-Me, 12·8; OMe, 13·7%). Direct comparison showed that the specimen was identical with that obtained by Iyer and Robinson (*J.*, 1934, 1635). The hydrochloride, picrate, and methiodide were also identical in properties when made from the two sources.

Hexahydroajmaline.—(*a*) Ajmaline (0·7 g.), dissolved in 50% acetic acid (30 c.c.), was hydrogenated in presence of Adams catalyst (0·72 g.). Absorption was rapid and stopped sharply after the uptake of 3 mols. of hydrogen. The filtered solution was made alkaline with ammonia. After some time the amorphous precipitate crystallised and was then collected (0·58 g.; m. p. 145—150°). On recrystallisation from aqueous ethanol *hexahydroajmaline* was obtained as plates, m. p. 120—122° (frothing), or after drying at 100° *in vacuo*, m. p. 149—150° with slight previous sintering. It did not give the ajmaline colour reactions (Found, in material dried at 100° *in vacuo*: C, 72·1, 71·9; H, 9·5, 9·4; *C*-Me, 4·7. $C_{20}H_{32}O_2N_2$ requires C, 72·2; H, 9·6; 1*C*-Me, 4·5%) and had $[\alpha]_D^{20}$ +92° (*c* 1·9 in $CHCl_3$).

(*b*) Ajmaline dihydrochloride (0·5 g.) in anhydrous methanol (30 c.c.) was shaken with Adams platinum oxide (50 mg.) in hydrogen, which was rapidly absorbed (87 c.c. after 1 hr. Calc. for 3 mols., 93 c.c.). The filtered solution was concentrated to about 10 c.c. and mixed with dry ether; the *dihydrochloride* crystallised as long needles when kept in the ice-chest for 24 hr. The crystals, washed with dry ether and dried, had m. p. (anhyd.) 302° (decomp.) (Found, in material dried at 100° *in vacuo*: Cl, 17·9. $C_{20}H_{32}O_2N_2$,2HCl requires Cl, 17·5%). The free base, generated from the hydrochloride in the usual way, melted at 150° after crystallisation from ethanol with the addition of a drop of water.

Diacetylhexahydroajmaline.—Hexahydroajmaline (0·5 g.) was refluxed with acetic anhydride (4 c.c.) and benzene (6 c.c.) for 6·5 hr. The solution was evaporated to dryness *in vacuo*, and the glassy residue dissolved in water. Addition of perchloric acid caused the separation of a crystalline perchlorate, which was washed with methanol [yield, 0·5 g.; m. p. 180° (frothing)]. It recrystallised from methanol–ether in colourless needles which sintered at 190° and decomposed at 265°.

The perchlorate was dissolved in water, and dilute aqueous ammonia was added. Extraction with ether gave a *diacetyl* derivative which after recrystallisation from light petroleum (b. p. 40—60°) had m. p. 131—132°, $[\alpha]_D$ +66° (*c* 2·4 in $CHCl_3$) (Found: C, 69·45; H, 8·8. $C_{24}H_{36}O_4N_2$ requires C, 69·2; H, 8·7%).

Hydrogenation of Diacetylajmaline.—Diacetylajmaline (0·201 g.) was hydrogenated in 50% acetic acid (20 c.c.) in presence of Adams catalyst (0·08 g.). After the uptake of 3 mols. of hydrogen, absorption ceased (1 hr.). The solution was filtered and made alkaline with ammonia. Extraction with ether gave a product, which on recrystallisation from light petroleum had m. p. 130—131°, undepressed by diacetylhexahydroajmaline.

On hydrolysis with methanolic potassium hydroxide it gave hexahydroajmaline, m. p. and mixed m. p. 150—151°.

Deoxydihydroajmaline.—Ajmaline (1·0 g.), hydrazine hydrate (3 c.c. of 90%), and diethylene glycol (8 c.c.) were refluxed for 10 min. Potassium hydroxide (0·4 g.) was then added and the temperature of the liquid raised to 195° by distillation. After 1·5 hr. at this temperature, the solution was cooled, diluted with water (50 c.c.), and, after 1 hr., filtered and the substance well washed with water, to give 0·82 g. (94%) of deoxydihydroajmaline, m. p. 182—184°. If the reaction is conducted in a stream of nitrogen the product is colourless, but in any case the *substance* is best purified by sublimation *in vacuo* followed by crystallisation from aqueous alcohol; it then has m. p. 185—186°, $[\alpha]_D$ +39° (*c* 2·5 in $CHCl_3$), pK_a 8·25 [Found: C, 77·3, 77·1; H, 9·2, 9·1; N, 8·9, 9·0; *C*-Me, 7·85; active H (at 20°), 0·41. $C_{20}H_{28}ON_2$ requires C, 76·9; H, 9·1; N, 9·0; 2*C*-Me, 9·6; 2H, 0·64%].

Acetyldeoxydihydroajmaline.—A solution of deoxydihydroajmaline (0·025 g.) in acetic anhydride (1 c.c.) was kept for 12 hr. The excess of anhydride was hydrolysed by water, and on further dilution a precipitate was formed, which was only slightly increased on neutralisation with dilute ammonia. The precipitated *acetate* was taken up in ether, but the residue left after evaporation of the solvent could not be crystallised. It gave a neutral solution in aqueous alcohol and only dissolved in moderately strong hydrochloric acid. It distilled as a colourless glass, b. p. 200°/0·005 mm., m. p. *ca.* 90° (Found: C, 74·9; H, 8·7. $C_{22}H_{30}O_2N_2$ requires C, 74·6; H, 8·5%).

Benzoyldeoxydihydroajmaline.—Deoxydihydroajmaline (0·65 g.), benzoyl chloride (0·35 c.c.), and 5% sodium hydroxide solution (20 c.c.) were mixed and well shaken for 2 hr. The insoluble *benzoyl* derivative crystallised from aqueous methanol as colourless needles (0·6 g.), m. p. 250—255° (Found, in material dried at 100° *in vacuo*: C, 78·0; H, 7·8. $C_{27}H_{32}O_2N_2$ requires C, 77·9; H, 7·8%). The substance reacts very slowly with methyl iodide in boiling acetone but the resulting methiodide could not be crystallised.

The quaternary reineckate was chromatographed from acetone solution on alumina and after conversion into the chloride exhibited none of the usual ajmaline colour reactions. Evidently N(*a*) has been quaternised in this case.

*Deoxydihydrotoluene-*p*-sulphonylajmaline.*—Deoxydihydroajmaline (0·1 g.) was dissolved in ether (5 c.c.) containing toluene-*p*-sulphonyl chloride (10% excess) and shaken overnight with 5% sodium hydroxide solution (1 c.c.). The ether was then separated and, after evaporation of the solvent, the residue crystallised from aqueous methanol as colourless needles (0·1 g.), m. p. 224—225°, pK_a 2·5. The *toluene-*p*-sulphonyl* derivative was insoluble in 1% hydrochloric acid, even on boiling, but it dissolved in hot 10% hydrochloric acid and was reprecipitated on addition of dilute ammonia (Found, in material dried at 100° *in vacuo* over P_2O_5: C, 69·8; H, 7·3; S, 6·6; active H, 0·26. $C_{27}H_{34}O_3N_2S$ requires C, 69·5; H, 7·4; S, 6·9; 1H, 0·22%).

*Deoxydihydro-*N*-methylajmaline Hydriodide.*—Deoxydihydroajmaline (0·08 g.) was kept for 2 hr. with methyl iodide (0·5 c.c.) and chloroform (2 c.c.). The mixture was then evaporated and the residue crystallised from methanol–ether, giving colourless prisms (1 g.), m. p. 260—264°. Recrystallised from the same solvent the *N-methyl hydriodide* was obtained as fine colourless needles which after drying at 100° *in vacuo* had m. p. 262—264° (Found: C, 55·3; H, 6·6; N, 6·3; I, 27·7. $C_{21}H_{30}ON_2$,HI requires C, 55·5; H, 6·9; N, 6·2; I, 27·9%). An aqueous solution of this salt gave an immediate precipitate with dilute ammonia, and this was completely soluble even in light petroleum but did not crystallise. The base dissolved readily in dilute hydrochloric acid and addition of potassium iodide caused crystallisation of the hydriodide, m. p. and mixed m. p. 262—264°.

Oxidation of Deoxydihydroajmaline to Ethyl Methyl Ketone.—Deoxydihydroajmaline (0·5 g.) in water (10 c.c.) and concentrated sulphuric acid (10 c.c.) was heated, under nitrogen, almost to the b. p. after chromium trioxide (5 g.) in water (10 c.c.) had been added. The distillate was collected in a saturated solution (15 c.c.) of 2 : 4-dinitrophenylhydrazine in dilute hydrochloric acid. After ½ hr. more chromium trioxide (5 g.) was added and the distillation continued slowly for a further ½ hr. The crystalline precipitate (37 mg.) was collected (m. p. 109—111°). The product, purified by chromatography on alumina from a benzene solution, and finally by crystallisation from aqueous methanol, had m. p. 115—116°, or 114—115° when mixed with authentic ethyl methyl ketone 2 : 4-dinitrophenylhydrazone of m. p. 114—115° (Found: C, 47·7; H, 5·0. Calc. for $C_{10}H_{12}O_4N_4$: C, 47·6; H, 4·8%).

*Deoxydihydroiso**ajmaline.*—*iso*Ajmaline (0·26 g.) was refluxed in an atmosphere of nitrogen, with diethylene glycol (6 c.c.) and 85% hydrazine hydrate (2 c.c.) for 10 min. Potassium hydroxide (0·2 g.) was then added and the temperature raised to 190° by distillation. After 2 hr. at this temperature the solution was diluted with water and boiled until the precipitate crystallised. The mixture was cooled and filtered, giving deoxydihydro*iso*ajmaline (0·22 g.), m. p. 152—153°. After sublimation *in vacuo* and crystallisation from aqueous methanol it had m. p. 153—154°, $[\alpha]_D^{20}$ +30° (*c*, 2·3 in $CHCl_3$) (Found: C, 76·2, 76·9, 77·4; H, 8·9, 9·4, 9·1; N, 9·0; *C*-Me, 8·4, 8·5; active H, 0·43. $C_{20}H_{28}ON_2$ requires C, 76·9; H, 9·1; N, 9·0; 2*C*-Me, 9·6; 2H, 0·64%).

*Deoxydihydro-*N*-methyliso**ajmaline Hydriodide.*—Deoxydihydro*iso*ajmaline (0·3 g.) was dissolved in benzene (15 c.c.), and methyl iodide (0·5 c.c.) added; crystals were deposited overnight. After decantation the *product* was recrystallised from methanol–ether, affording colourless needles (0·35 g.), m. p. 284—287° (decomp.) (Found: C, 55·6; H, 6·9; I, 28·0. $C_{21}H_{30}ON_2$,HI requires C, 55·5; H, 6·9; I, 27·6%). An aqueous solution of this salt gave an immediate precipitate with dilute ammonia. The *base* so obtained was recrystallised twice

from aqueous methanol and had m. p. 129—130°, $[\alpha]_D$ +100° (*c*, 2·4 in $CHCl_3$) (Found: C, 77·2; H, 9·1; N, 8·9. $C_{21}H_{30}ON_2$ requires C, 77·3; H, 9·3; N, 8·6%). Addition of potassium iodide to a solution of the base in dilute hydrochloric acid regenerated the hydriodide, m. p. and mixed m. p. 284—287°.

Oxidation of Deoxydihydroisoajmaline to Ethyl Methyl Ketone.—Deoxydihydro*iso*ajmaline (0·2 g.) was oxidised as was the corresponding ajmaline derivative. The crude 2 : 4-dinitrophenylhydrazone (10 mg.) had m. p. 108—109°. After chromatography on alumina, orange crystals were obtained, having m. p. 114—115°, undepressed by admixture with authentic ethyl methyl ketone 2 : 4-dinitrophenylhydrazone of the same m. p.

Deoxyoctahydroajmaline.—A mixture of hexahydroajmaline (0·3 g.), diethylene glycol (4 c.c.), and 90% hydrazine hydrate (1 c.c.) was refluxed for 5 min., and then potassium hydroxide was added. The product (0·27 g.), isolated as in the previous experiment, had m. p. 187—189°; it sublimed readily, even at atmospheric pressure, and then had m. p. 188—189°, $[\alpha]_D^{20}$ +89° (*c*, 1·8 in $CHCl_3$). It showed only end-absorption in the ultra-violet (Found: C, 75·6; H, 10·9; N, 9·0; active H, 0·45, 0·44; *C*-Me, 9·15. $C_{20}H_{34}ON_2$ requires C, 75·7; H, 10·8; N, 8·8; 2H, 0·66; 2*C*-Me, 9·7%).

Deoxyoctahydroajmaline was also prepared by catalytic reduction of deoxydihydroajmaline. Experiments with palladised charcoal in neutral solution showed no absorption of hydrogen, and only very slow absorption in the presence of acetic acid, but Adams catalyst gave satisfactory results. Deoxydihydroajmaline (0·117 g.) was dissolved in 50% acetic acid (40 c.c.) and hydrogenated at room temperature and pressure in the presence of Adams catalyst (0·08 g.). Absorption of 3 mols. of hydrogen took place in 25 min. after which there was no further uptake. The filtered solution was made alkaline with ammonia and then extracted with ether. The residue, on evaporation of the solvent, crystallised (m. p. 184—188°), and after recrystallisation from aqueous methanol was obtained as long fine needles, m. p. 188—189° undepressed by deoxyoctahydroajmaline prepared from hexahydroajmaline.

Attempted Oxidation of Deoxyoctahydroajmaline.—Deoxyoctahydroajmaline (0·1 g.), dissolved in glacial acetic acid (4 c.c.), was treated with a solution of chromium trioxide (0·1 g.) in water (0·5 c.c.) and acetic acid (2 c.c.). The mixture was set aside at room temperature for 30 hr., then made strongly alkaline and extracted with chloroform. The residue after evaporation of the solvent was passsed in benzene through a column of alumina. Elution did not occur with ether alone, but ether containing 2% of methanol eluted starting material, which after crystallisation from aqueous methanol had m. p. and mixed m. p. 189—190°.

Action of Bromine on Deoxyoctahydroajmaline.—Deoxyoctahydroajmaline (0·1 g.) was dissolved in hydrobromic acid (1 c.c.) containing bromine (1 c.c.). The dark red mixture was set aside overnight, then diluted with water and boiled to expel the bromine, the last traces of which were removed with a little sodium sulphite. On addition of ammonia crystalline unchanged starting material, m. p. and mixed m. p. 188—189°, was obtained.

Action of 50% Sulphuric Acid on Deoxyoctahydroajmaline.—Deoxyoctahydroajmaline (0·2 g.) was heated on a steam-bath with 50% sulphuric acid (10 c.c.) for 1 hr. The base, obtained in the usual way and crystallised from acetone, was unchanged starting material (m. p. and mixed m. p. 188—189°).

Action of Thionyl Chloride on Deoxyoctahydroajmaline.—A solution of this base (0·1 g.) in concentrated hydrochloric acid (1 c.c.) was evaporated to dryness *in vacuo*, and the residue dissolved in a mixture of chloroform (5 c.c.) and thionyl chloride (5 c.c.). After refluxing for 4 hr., the solution was evaporated to dryness and the solid crystallised from methanol–ether. The colourless needles of *deoxyoctahydroajmaline dihydrochloride* had m. p. *ca.* 350° (with frothing) (Found: C, 61·1; H, 9·3; Cl, 20·0. $C_{20}H_{34}ON_2,2HCl$ requires C, 61·5; H, 9·3; Cl, 18·1%). The base had m. p. 188—189°, undepressed by deoxyoctahydroajmaline.

Hexahydroisoajmaline.—Hexahydroajmaline (0·5 g.) was refluxed in methanol (25 c.c.) with sodium hydroxide (0·5 g.) for 5 hr. The solution was evaporated to a small bulk *in vacuo*, water was added, and the oil was extracted with ether. The dried (Na_2SO_4) extract left *hexahydroisoajmaline* as an oil on evaporation; this did not crystallise readily, but when an ethereal solution was kept at 0° large, colourless, elongated prisms, containing ether of crystallisation, gradually separated. The crystals had m. p. *ca.* 110° (frothing), or *ca.* 210° solvent-free. For analysis the substance was sublimed *in vacuo*, then having m. p. 208—210° with sintering at 206°, $[\alpha]_D^{19}$ +73° (*c* 2·15 in $CHCl_3$) (Found: C, 72·4; H, 9·7. $C_{20}H_{32}O_2N_2$ requires C, 72·3; H, 9·7%).

Deoxyoctahydroisoajmaline.—Hexahydro*iso*ajmaline (0·05 g.) was reduced in the usual way, with diethylene glycol (1 c.c.), hydrazine hydrate (0·2 c.c.), and potassium hydroxide (0·1 g.).

The *deoxy*-compound obtained on dilution of the reaction mixture was crystalline and after sublimation *in vacuo* formed colourless prisms, m. p. 184—186·5°, mixed m. p. with deoxyoctahydroajmaline 175—180°, $[\alpha]_D^{19}$ +115° (*c*, 1·0 in $CHCl_3$) (Found: C, 75·3; H, 10·6. $C_{20}H_{34}ON_2$ requires C, 75·7; H, 10·8%).

Wolff–Kishner Reduction of Ajmaline Methiodide.—Ajmaline methiodide (0·5 g.) was reduced in the usual way with diethylene glycol (5 c.c.), hydrazine hydrate (1·5 c.c.), and potassium hydroxide (0·5 g.). The product obtained by dilution with water and ether-extraction was a colourless glass (0·35 g.). On dissolving in dilute hydrochloric acid it readily gave crystalline *deoxydihydro-N-methylajmaline hydrochloride*, m. p. 272—277°, $[\alpha]_D^{18·5}$ +61° (*c*, 2·3 in H_2O) (Found: C, 69·6; H, 8·5; Cl, 10·0. $C_{21}H_{30}ON_2$,HCl requires C, 69·5; H, 8·6; Cl, 9·8%).

The *base*, regenerated from the hydrochloride was sublimed *in vacuo*, then forming a colourless glass, $[\alpha]_D^{18}$ +66° (*c*, 2·43 in $CHCl_3$) (Found: C, 77·2; H, 9·3; active H, 0·29. $C_{21}H_{30}ON_2$ requires C, 77·3; H, 9·3; 1H, 0·31%).

The hydriodide, obtained from an aqueous solution of the hydrochloride on addition of potassium iodide, formed colourless needles, m. p. 262—264°, unchanged by admixture with deoxydihydro-*N*-methylajmaline hydriodide.

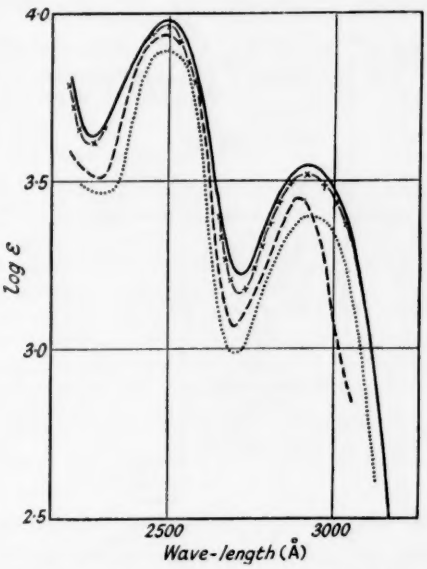
Deoxydihydro-N-methylajmaline Methiodide.—Deoxydihydro-*N*-methylajmaline, obtained by Wolff–Kishner reduction of ajmaline methiodide (5 g.), was dissolved in methyl iodide (20 c.c.) and kept for 2 days. The residue after evaporation crystallised slowly from methanol–ether as glistening, compact prisms (3·0 g.), m. p. 213—215° (frothing) and with previous sintering at 200° (Found: C, 55·6; H, 7·4; N, 5·5. $C_{22}H_{33}ON_2I$, CH_4O requires C, 55·2; H, 7·5; N, 5·6%). The *methiodide* did not crystallise from aqueous solvents. Its aqueous solution gave no precipitate with ammonia. When pyrolysed over a free flame in a test tube at 15 mm. pressure it decomposed with vigorous gas evolution, leaving a colourless oil, which was identified as deoxydihydro-*N*-methylajmaline by conversion into the crystalline hydrochloride, m. p. and mixed m. p. 272—275°.

Attempted Hofmann Degradation of Deoxydihydro-N-methylajmaline.—The methiodide (1 g.) was treated with an excess of silver oxide in hot water (100 c.c.), and the glassy methohydroxide left after removal of water from the filtered solution was heated at 180°/20 mm. for 10 min. The colourless oil eluted by chloroform from an alumina adsorbate was dissolved in dilute hydrochloric acid and converted into its hydriodide by addition of successive portions of potassium iodide; some of the fractions crystallised (40 mg.; m. p. 235—240°) and after recrystallisation, had m. p. 250—255° alone or mixed with deoxydihydro-*N*-methylajmaline hydriodide (Found: C, 55·9; H, 7·1. Calc. for $C_{21}H_{30}ON_2$,HI: C, 55·5; H, 6·9%). The infra-red spectra of the two specimens were identical. It is certain that the methohydroxide simply lost the elements of methanol but the yield was low and the process will be re-investigated.

Anhydrohexahydroajmaline Oxime.—Hexahydroajmaline oxime (0·55 g.) was dissolved in a mixture of acetic anhydride (1 c.c.) and acetic acid (2 c.c.). The mixture was saturated with dry hydrogen chloride without cooling, and set aside. Colourless needles (0·5 g.) of *O-acetylanhydrohexahydroajmaline oxime dihydrochloride* separated and after recrystallisation from methanol–ether had m. p. 350—352° (decomp.) (Found, in material dried at room temperature *in vacuo* over P_2O_5: C, 59·3; H, 8·1; Cl, 15·3. $C_{22}H_{35}O_2N_3Cl_2$ requires C, 59·5; H, 8·0; Cl, 16·0%). It was boiled with potassium hydroxide (0·3 g.) in methanol (12 c.c.) for 3 min., then the mixture was diluted with water, causing the separation of beautiful, flat needles of *anhydrohexahydroajmaline oxime*, m. p. 199—200°. For analysis the substance was sublimed *in vacuo*; it then had $[\alpha]_D^{17·5}$ +44° (*c*, 2·03 in $CHCl_3$) (Found: C, 72·5; H, 9·4. $C_{20}H_{31}ON_3$ requires C, 72·9; H, 9·5%).

Action of Methyl Iodide on N-Methyl-sec.-ajmaline.—Ajmaline methiodide (0·2 g.), dissolved in water (20 c.c.), was made alkaline with excess of 10% sodium hydroxide solution and then extracted with chloroform (4 × 10 c.c.). The extract, after drying (Na_2SO_4), was evaporated *in vacuo* at as a low temperature as possible. The residue was freed from water and chloroform by distillation with benzene *in vacuo*. It was then dissolved in methyl iodide (5 c.c.) and the solution kept for 30 hr. The excess of the reagent was evaporated and the partly solid residue crystallised from hot water containing a little potassium iodide. The product was obtained as small prisms (0·15 g.), m. p. 250° (decomp.), which, after several recrystallisations from water with the addition of potassium iodide, and finally from water alone, had m. p. 251—252° (decomp.) (Found: C, 54·9; H, 6·5; I, 25·3; OMe, 8·0; NMe, 5·2. $C_{22}H_{31}O_2N_2I$ requires C, 54·8; H, 6·5; I, 26·3; 1OMe, 6·4; 1NMe, 6·0%). The *salt* showed true quaternary character, and could even be crystallised unchanged from concentrated potassium hydroxide solution. Further estimations of OMe and NMe combined gave values of 12—15% calculated as *N*-Me.

Dihydro-N-methylajmaline Hydriodide.—*N*-Methyl-*sec.*-ajmaline, prepared as before from ajmaline methiodide (1 g.) and dried by distillation with benzene *in vacuo*, was dissolved in tetrahydrofuran (30 c.c.), and the solution carefully added to a suspension of lithium aluminium hydride (0·5 g.) in the same solvent (20 c.c.). The mixture was refluxed for 2 hr. and then cautiously decomposed by the addition of water. The solution was filtered and the granular precipitate washed with tetrahydrofuran. The combined filtrate and washings, on evaporation to dryness, left a colourless oil, which did not crystallise but readily afforded a crystalline hydriodide (0·5 g.) on addition of potassium iodide to a solution in dilute hydrochloric acid. The *hydriodide* formed colourless needles, easily soluble in hot water, and had m. p. 224—226° (frothing) (Found, in material dried at 100°: C, 53·8; H, 6·4. $C_{21}H_{30}O_2N_2,HI$ requires C, 53·6; H, 6·7%). The same product was obtained more easily by adding a concentrated aqueous solution of potassium borohydride (0·2 g.) to a warm solution of ajmaline methiodide (1·5 g.) in water (50 c.c.). The base was precipitated as an oil almost immediately. The mixture was acidified with dilute hydrochloric acid, and the hydriodide (1 g.) obtained by the addition of potassium iodide.



····· Ajmaline.
— — — *iso*Ajmaline.
——— Anhydroajmaline oxime.
×–×–× Anhydro*iso*ajmaline oxime.

Deoxyajmaline.—Dihydro-*N*-methylajmaline hydriodide (1 g.) was refluxed with hydrobromic acid (20 c.c. of 50%) for 4 hr. The solution was then evaporated to dryness *in vacuo*, and the residue dissolved in water and mixed with a saturated solution of Reinecke's salt (5 g.). The amorphous precipitate was dried and adsorbed on alumina from an acetone solution. The most readily eluted and major fraction was concentrated *in vacuo*, and diluted with warm water; long needles separated on cooling. The reineckate was collected, dissolved in acetone, and converted into the chloride by successive treatments with silver sulphate and barium chloride. The filtered solution was evaporated to dryness *in vacuo* and the residue washed with boiling alcohol, which left the barium chloride undissolved. The alcoholic solution was diluted with ether, colourless needles of *deoxyajmaline methochloride* being deposited. The salt was recrystallised from methanol–ether and formed long, colourless needles, m. p. 305—310° (decomp.) (Found: C, 64·5; H, 8·7. $C_{21}H_{29}ON_2Cl,CH_4O,H_2O$ requires C, 64·3; H, 8·6%). *Deoxyajmaline methobromide* was obtained on addition of sodium bromide to an aqueous solution of the methochloride. It crystallised from methanol–ether in colourless prisms, m. p. 320—325°, $[\alpha]_D^{20}$ +132° (*c*, 1·44 in H_2O) (Found: C, 61·6; H, 7·4; Br, 19·0. $C_{21}H_{29}ON_2Br,0{\cdot}5CH_4O$ requires C, 61·3; H, 7·4; Br, 19·0%).

Deoxyajmaline methochloride was pyrolysed in a test tube at 0·5 mm. pressure, over a free flame. Colourless crystals sublimed on the cold parts of the tube. The product, *deoxyajmaline*, recrystallised from aqueous methanol as colourless plates, m. p. *ca.* 310° (sublimation), $[\alpha]_D^{20}$

+124° (*c*, 0·94 in MeOH–$CHCl_3$, 5 : 2 by vol.) (Found : C, 76·9; H, 8·2. $C_{20}H_{26}ON_2$ requires C, 77·4; H, 8·4%).

Physical Data.—Values of pK_a were determined in 80% Methylcellosolve except where stated otherwise, at 18—20°, with a glass electrode and Cambridge pH meter and at concentrations of about M/100. 0·1N-Hydrochloric acid was used in the titrations.

The ultra-violet absorptions of ajmaline and *iso*ajmaline (and their anhydro-oximes) were very similar (see Figure).

Hexahydroajmaline and deoxyoctahydroajmaline showed only end-absorption (at *ca.* 2000 Å).

Active-hydrogen values were determined at room temperature. Under these conditions the NH group usually affords about 30% of the theoretical value.

Infra-red absorption bands of paraffin-paste suspensions (Perkin-Elmer double-beam instrument; wave-lengths in microns) are tabulated below.

Substance	Selected bands or no band	Interpretation *
Ajmaline	3·00, 3·17	OH
	3·5—4·00	Bonded OH
	6·21	*
*iso*Ajmaline	2·85, 3·27	OH
	3·5—3·8	Bonded OH
	—	No CO
	6·21	*
Hexahydro-ajmaline	3·10 (wide)	OH
	—	No CO or substituted benzene
Ajmaline hydrochloride	2·95, 3·03, 3·14	Various OH
	3·5—4·00	,,
	6·00 (weak)	?
	6·19	*
Do., $2H_2O$	2·83, 3·02, 3·06	OH
	3·15, 3·50—4·00	,,
	(6·04 (medium)	?
	6·20	*
Ajmaline dihydrochloride	3·10, 3·25	OH
	3·5—4·25	,,
	—	No CO
	—	No benzene band (!)
Diacetylajmaline	—	No OH
	5·75	CO of OAc
	—	No CO of NAc
	6·21	*
Diacetylhexahydroajmaline	—	No OH
	3·72, 5·76	CO of OAc
	—	No CO of NAc
	—	No benzene band
Deoxydihydro-ajmaline	3·20	OH
	6·21	*
Deoxydihydro*iso*-ajmaline	3·15	OH
	6·21	*
Deoxyoctahydro-ajmaline	3·05, 3·23	OH
	—	No benzene band
Deoxydihydro-*N*-methyl*iso*-ajmaline	3·05	OH
	6·20	*
Ajmaline methiodide	2·98, 3·10	OH
	—	No CO
	6·20	*
*iso*Ajmaline methiodide	2·77, 2·98, 3·27	OH
	—	No CO
	6·20	*
N-Methylajmaline hydrate	2·97	OH
	5·97, 6·04	†
	6·20	*
N-Methylajmaline (distilled) (contains some methyl*iso*-ajmaline)	2·97	OH
	5·80 (strong)	Unconjugated CO
	5·92 (weak)	Conjugated CO
	6·20	*
	>7·0	Follows the curve of its hydrate
Do. in $CHCl_3$	5·81 (weak), 5·93 (strong)	As above
N-Methyl*iso*-ajmaline	Similar results	As above
*iso*Ajmaline oxime	3·00, 3·05	OH
	—	No :C=N·
	6·20	*
Ajmaline oxime hydrochloride	2·90, 3·00, 3·05	OH
	6·15	:C=N· (?)
Hexahydro-ajmaline oxime	3·10, 3·30, 3·55	OH
	6·05	:C=N·
	—	No benzene band
Anhydroajmaline oxime	3·20	OH
	4·50	CN
	—	No CO
	6·22	*
Anhydro*iso*-ajmaline oxime	3·0, 3·12	OH
	4·47	CN
	—	No CO
	6·20	*

* In this column an asterisk denotes an aromatic benzene nucleus.
† Small separation to double peak, conjugated CO.

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Reactions of Fluorocarbon Radicals. Part XV. Synthesis and Hydration of* 1 : 1 : 1-*Trifluorobut-2-yne.*

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1 : 1 : 1-Trifluorobut-2-yne has been synthesised from trifluoroiodomethane and propyne *via* 1 : 1 : 1-trifluoro-3-iodobut-2-ene and 2 : 3-dibromo-1 : 1 : 1-trifluorobut-2-ene. Hydration of the butyne catalysed by a mercury salt yields only 4 : 4 : 4-trifluorobutan-2-one, and the significance of this on the mechanism of hydration of acetylenes is discussed.

In Parts VI and VII (*J.*, 1952, 3483, 3490) the reaction of HX (X = F, Cl, Br, I, OMe, OEt, or NR_2) with 3 : 3 : 3-trifluoropropyne under conditions favouring a reaction with ionic intermediates was shown to yield $CF_3{\cdot}CH{:}CHX$, *i.e.*, there was a reversal of the direction of addition with respect to propyne, indicating a polarisation $F_3C \longleftarrow \overset{\delta-\ \delta+}{C{:}CH}$. Hydration of trifluoropropyne was thus expected to yield exclusively the aldehyde $CF_3{\cdot}CH_2{\cdot}CHO$, but it was found that a mixture of the aldehyde and the ketone $CF_3{\cdot}CO{\cdot}CH_3$ was produced in the ratio 1 : 2 :

$$CF_3{\cdot}C{:}CH \longrightarrow CF_3{\cdot}CH_2{\cdot}CHO + CF_3{\cdot}CO{\cdot}CH_3$$

Since a mercury-salt catalyst was essential to bring about hydration, it was suggested that two competing reactions were involved in the hydration of an acetylene $R{\cdot}C{:}CH$ (R = electron-withdrawing group such as CF_3, C_2F_5, or COPh) : (*a*) formation of the aldehyde *via* an intermediate complex formed by addition of the mercury salt to the triple bond, and (*b*) formation of the ketone *via* a compound of the type $R{\cdot}C{:}C{\cdot}HgY$ (Y = HSO_4, say, in sulphuric acid solution). Full details are given in Part VI (*loc. cit.*). Since the acetylenic hydrogen atom is essential in scheme (*b*), the catalysed hydration of 1 : 1 : 1-trifluorobut-2-yne should take place in the direction predicted from the inductive effects of the methyl and the trifluoromethyl and yield only 4 : 4 : 4-trifluorobutan-2-one :

$$CF_3{\cdot}C{:}C{\cdot}CH_3 \longrightarrow CF_3{\cdot}CH_2{\cdot}CO{\cdot}CH_3$$

Trifluoroiodomethane reacts with propyne when exposed to ultra-violet light, to give 1 : 1 : 1-trifluoro-3-iodobutene :

$$CF_3{\cdot} + CH_3{\cdot}C{:}CH \longrightarrow CH_3{\cdot}\dot{C}{:}CH{\cdot}CF_3 \xrightarrow{CF_3I} CH_3{\cdot}CI{:}CH{\cdot}CF_3 + CF_3{\cdot}$$

This compound reacts vigorously with bromine at low temperature to give, by addition to the double bond and replacement of iodine, 2 : 2 : 3-tribromo-4 : 4 : 4-trifluorobutane. Dehydrobromination of the tribromo-compound is predominantly in one direction to give 2 : 3-dibromo-1 : 1 : 1-trifluorobutene, since the hydrogen atom α to the trifluoromethyl group is preferably eliminated as a proton (see *J.*, 1951, 2495); debromination of the dibromotrifluorobutene completes the synthesis :

$$CF_3{\cdot}CH{:}CI{\cdot}CH_3 \xrightarrow{Br_2} CF_3{\cdot}CHBr{\cdot}CBr_2{\cdot}CH_3 \xrightarrow{-HBr} CF_3{\cdot}CBr{:}CBr{\cdot}CH_3$$

$$CF_3{\cdot}CBr{:}CBr{\cdot}CH_3 \xrightarrow{Zn\text{-}EtOH} CF_3{\cdot}C{:}C{\cdot}CH_3$$

The 1-alkyne, 4 : 4 : 4-trifluorobut-1-yne, is a major impurity in the product, and is easily detected by its characteristic infra-red spectrum, and notably the acetylenic C–H band at 3·0 μ. It is formed by isomerisation during the debromination step, but can be separated from the but-2-yne by formation of the silver or copper acetylide.

If the temperature is allowed to rise too high during the initial bromination step, hydrogen bromide is evolved and unidentified polybromo-compounds are formed.

The dehydrobromination step is best effected at *ca.* 0° since at higher temperatures two dibromotrifluorobutenes, which could not be separated by distillation on the scale used,

* Part XIV, Haszeldine and Jander, *J.*, 1954, 919.

are formed. Infra-red spectroscopic examination shows that one is 2 : 3-dibromo-1 : 1 : 1-trifluorobut-2-ene which, when pure, has only one C:C stretching vibration in the 6-μ region (6·18 μ); the other is 2 : 3-dibromo-4 : 4 : 4-trifluorobut-1-ene, since a second C:C stretching vibration at 6·05 μ and a vinylic C–H stretching vibration band at 3·25 μ can be observed in the spectrum of the mixture, *i.e.* :

$$CF_3{\cdot}CHBr{\cdot}CBr_2{\cdot}CH_3 \longrightarrow CF_3{\cdot}CBr{:}CBr{\cdot}CH_3 + CF_3{\cdot}CHBr{\cdot}CBr{:}CH_2$$

Since debromination of the mixture gives only the trifluorobut-1- and -2-yne as volatile products, it appears that either the trifluoromethylallene expected from 2 : 3-dibromo-4 : 4 : 4-trifluorobut-1-ene is isomerised to the alkynes, or the second dibromo-compound yields products which do not contaminate the alkyne fraction. The compound $CF_3{\cdot}CH{:}C{:}CH_2$ has been synthesised by an alternative route (B. R. Steele, unpublished work), and comparison of infra-red spectra shows that it is not formed in the above debromination. It should be noted that debromination of *pure* 2 : 3-dibromo-1 : 1 : 1-trifluorobutene gives a mixture of the two butynes.

Dehydrobromination is incomplete at temperatures below 0° and 2-bromo-4 : 4 : 4-trifluorobut-2-ene then becomes a major product :

$$CF_3{\cdot}CH{:}CI{\cdot}CH_3 \xrightarrow{Br_2} CF_3{\cdot}CHBr{\cdot}CBr_2{\cdot}CH_3 \xrightarrow{Zn\text{–}EtOH} CF_3{\cdot}CH{:}CBr{\cdot}CH_3$$

This compound shows C:C stretching absorption at 6·00 μ (cf. $CF_3{\cdot}CH{:}CH{\cdot}CH_3$, 5·90 μ; $CF_3{\cdot}CH{:}CCl{\cdot}CF_3$, 5·98 μ; $CF_3{\cdot}CH{:}CI{\cdot}CF_3$, 6·07 μ; *trans*-isomers).

The effect of hydrogen substitution on the boiling point of fluoroacetylenes is shown in the annexed Table. Replacement of three hydrogen atoms in but-2-yne by fluorine causes

	B. p.		B. p.		B. p.		B. p.
$CH_3{\cdot}C{:}C{\cdot}CH_3$	27·2°	*trans*-$CH_3{\cdot}CH{:}CH{\cdot}CH_3$	2·5°	$CH_3{\cdot}C{:}CH$ ...	−23°	$CH_3{\cdot}CH{:}CH_2$...	−48°
$CF_3{\cdot}C{:}C{\cdot}CH_3$	18·5	,, $CF_3{\cdot}CH{:}CH{\cdot}CH_3$	16·5	$CF_3{\cdot}C{:}CH$ ...	−48	$CF_3{\cdot}CH{:}CH_2$...	−22
$CF_3{\cdot}C{:}C{\cdot}CF_3$	−25	,, $CF_3{\cdot}CH{:}CH{\cdot}CF_3$	9				

only a slight decrease in boiling point (9°), but replacement of the remaining three hydrogen atoms causes a very marked decrease (43°); the corresponding variation in boiling point in the but-2-ene series is much smaller. The corresponding propyne and propene compounds are also shown in the Table (see earlier papers for details).

The acetylenic carbon–hydrogen stretching vibration is at 3·04 μ in propyne, and is shifted appreciably to shorter wave-length (3·01 μ) in fluorine-substituted alk-1-ynes, as shown in the following Table.

	C:C	C–H		C:C	
$CH_3{\cdot}C{:}CH$	4·63	3·04	$CH_3{\cdot}C{:}C{\cdot}CH_3$	4·47 4·33	} Raman
$CF_3{\cdot}C{:}CH$	4·65	3·01	$CF_3{\cdot}C{:}C{\cdot}CH_3$	4·34(m) 4·40(s)	} doublet
$C_2F_5{\cdot}C{:}CH$	4·66	3·01	$CF_3{\cdot}C{:}C{\cdot}CF_3$	4·23	probably

Monosubstituted acetylenes with fluorine on the α-carbon atoms show a C:C stretching vibration at longer wave-length than that of propyne, and this can be attributed to hyperconjugation involving fluorine, *e.g.*, $CF_3{\cdot}C{:}CH \longleftrightarrow F^- CF_2{:}C{:}CH^+$. When the triple bond is flanked by one or two trifluoromethyl groups as in 1 : 1 : 1-trifluoro- or hexafluoro-but-2-yne, its stretching vibration moves to shorter wave-length, as would be predicted from the inductive effect.

1 : 1 : 1-Trifluorobut-2-yne fails to react with aqueous sulphuric acid even when catalytic amounts of mercuric sulphate are added. When greater than molar quantities of the mercury salt are used, the formation of an intermediate solid complex can be observed. This is not completely decomposed to the ketone when heated, but only 4 : 4 : 4-trifluorobutan-2-one (b. p. 95°) is produced. The isomeric 1 : 1 : 1-trifluorobutan-2-one, which would be formed by addition in the opposite direction, has been prepared from reaction of trifluoromethylmagnesium iodide with propionyl chloride or ethyl propionate; it boils at 46°, and would thus be readily separated from 4 : 4 : 4-trifluorobutan-2-one. The products from the hydration were examined by infra-red spectroscopy for the carbonyl groups : 4 : 4 : 4-trifluorobutan-2-one shows the C:O stretching vibration at 5·72 μ, the characteristic position for compounds of the type $CF_3{\cdot}[CF_2]_n{\cdot}CH_2{\cdot}CO{\cdot}Alk$ (cf. Alk·CO·Alk, 5·75 μ).

The C:O stretching vibration in the known 1 : 1 : 1-trifluorobutan-2-one is at 5·62 μ (cf. $CF_3{\cdot}CO{\cdot}CH_3$, 5·61 μ), showing the characteristic shift to shorter wave-length; this shift is a maximum in compounds of the type $CF_3{\cdot}[CF_2]_n{\cdot}CO{\cdot}[CF_2]_n{\cdot}CF_3$, where the C:O vibration is at 5·56 μ. The spectroscopic examination failed to reveal any 1 : 1 : 1-trifluorobutan-2-one, or the presence of more than one carbonyl-containing compound.

4 : 4 : 4- and 1 : 1 : 1-Trifluorobutan-2-one cannot be distinguished by their ultra-violet spectra, which are very similar (see Table below), but the ketones give 2 : 4-dinitrophenylhydrazones which are easily distinguished by their melting points and by their ultra-violet spectra, as shown in the annexed Table. Examination of the ultra-violet and infra-red

	Solvent	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$
$CF_3{\cdot}CO{\cdot}C_2H_5$	Vapour	286·5	8·9	236·5	2·2
$CF_3{\cdot}CH_2{\cdot}CO{\cdot}CH_3$	Vapour	286	7·5	242	2·9
$CF_3{\cdot}CO{\cdot}C_2H_5$ 2 : 4-dinitrophenylhydrazone, m. p. 93°	EtOH	336	20,000	288	4,500
		254	12,000	238	11,400
		220	13,500	—	—
$CF_3{\cdot}CH_2{\cdot}CO{\cdot}CH_3$ 2 : 4-dinitrophenylhydrazone, m. p. 131—132°	EtOH	350	19,900	291	2,500
		225	14,500	Inflection 249	11,000

spectra of 2 : 4-dinitrophenylhydrazones prepared from various fractions of the hydration product showed that only 4 : 4 : 4-trifluorobutan-2-one was present. Control experiments showed that 1 : 1 : 1-trifluorobut-2-yne does not isomerise to 4 : 4 : 4-trifluorobut-1-yne under the conditions used, *i.e.*, the ketone isolated does not arise by $CF_3{\cdot}C{:}C{\cdot}CH_3 \longrightarrow CF_3{\cdot}CH_2{\cdot}C{:}CH \longrightarrow CF_3{\cdot}CH_2{\cdot}CO{\cdot}CH_3$.

The polarisation of 1 : 1 : 1-trifluorobut-2-yne during attack by an ionic reagent is $CF_3{\cdot}\overset{\delta-}{C}{\equiv}\overset{\delta+}{C}{\cdot}CH_3$, since reaction with hydrogen chloride in presence of aluminium chloride yields 2-chloro-4 : 4 : 4-trifluorobut-2-ene, which is identical with the product prepared from 1 : 1 : 1-trifluoro-3-iodobut-2-ene :

$$CF_3{\cdot}C{:}C{\cdot}CH_3 \xrightarrow[AlCl_3]{HCl} CF_3{\cdot}CH{:}CCl{\cdot}CH_3$$

$$CF_3{\cdot}CH{:}CI{\cdot}CH_3 \xrightarrow{Cl_2} CF_3{\cdot}CHCl{\cdot}CCl_2{\cdot}CH_3 \xrightarrow{Zn\text{–}EtOH} CF_3{\cdot}CH{:}CCl{\cdot}CH_3$$

The ketone formed by the hydration of 1 : 1 : 1-trifluorobut-2-yne is thus that predicted from the inductive effects of the trifluoromethyl and methyl groups :

$$CF_3{\cdot}\overset{\delta-}{C}{\equiv}\overset{\delta+}{C}{\cdot}CH_3 \xrightarrow{HgY_2} CF_3{\cdot}C(HgY){:}CY{\cdot}CH_3 \xrightarrow[-HgY_2]{+H_2O} CF_3{\cdot}CH{:}C(OH){\cdot}CH_3 \rightleftharpoons CF_3{\cdot}CH_2{\cdot}CO{\cdot}CH_3$$

where Y = HSO_4, say, in acid solution. This gives appreciable support to the ideas put forward in Part VI to explain the apparently anomalous hydration of perfluoroalkylacetylenes, and it should be noted that these ideas can be applied to any acetylene, not necessarily containing fluorine.

Experimental

1 : 1 : 1-*Trifluoro*-3-*iodobut*-2-*ene*.—Trifluoroiodomethane (28·7 g., 0·15 mole; for preparation see *J.*, 1951, 584), mixed with propyne (5·83 g., 0·15 mole) in a sealed 200-ml. Pyrex tube and exposed to ultra-violet radiation for 17 hr., gave 1 : 1 : 1-trifluoro-3-iodobut-2-ene (31·3 g., 91%), b. p. 95·0°, n_D^{20} 1·4352 (cf. Leedham and Haszeldine, *J.*, 1954, in the press).

2 : 3-*Dibromo*-1 : 1 : 1-*trifluorobut*-2-*ene*.—In a typical experiment 1 : 1 : 1-trifluoro-3-iodobut-2-ene (11·32 g., 0·05 mole) was cooled to −40° to −20° in a flask fitted with stirrer and reflux condenser, and to it was added dropwise (4 hr.) bromine (16·00 g., 0·10 mole); the reaction is vigorous if the temperature is allowed to rise. A slight excess of 25% ethanolic potassium hydroxide was then added dropwise at −10°, followed by an excess of 10% aqueous sulphuric acid. The lower layer (9·70 g., 76%) was distilled from phosphoric anhydride, to give 2 : 3-*dibromo*-1 : 1 : 1-*trifluorobut*-2-*ene*, b. p. 133—134° with partial decomposition (Found : C, 18·0; H, 1·2. $C_4H_3Br_2F_3$ requires C, 18·0; H, 1·1%). In other experiments the bromo-compound was distilled under reduced pressure, and had b. p. 62°/71 mm., 57·5°/45 mm., n_D^{19} 1·4568.

A by-product was 3-*bromo*-1 : 1 : 1-*trifluorobut*-2-*ene* (16%), b. p. 79—82°, n_D^{20} 1·403 (Found :

C, 25·6; H, 2·0%; *M*, 188. $C_4H_4BrF_3$ requires C, 25·4; H, 2·1%; *M*, 189). Other by-products (probably ethers formed during reaction with ethanolic potassium hydroxide) were not investigated.

1 : 1 : 1-*Trifluorobut-2-yne*.—2 : 3-Dibromo-1 : 1 : 1-trifluorobut-2-ene (2·0 g.) was added dropwise (1 hr.) to zinc (6 g.) and refluxing ethanol (20 ml.), and refluxing was continued for a further 8 hr. The volatile products passed through a reflux condenser and were condensed in traps cooled by liquid oxygen. Distillation *in vacuo* gave a mixture (0·60 g., 75%) of 1 : 1 : 1-trifluorobut-2-yne and 4 : 4 : 4-trifluorobut-1-yne (Found: *M*, 109. Calc. for $C_4H_3F_3$: *M*, 108). An experiment with 4·04 g. of the bromo-compound gave an 81% yield of the mixed alkynes.

The 4 : 4 : 4-trifluorobut-1-yne was removed by passing the mixed alkynes through aqueous-ethanolic silver nitrate (3 times) and ammoniacal cuprous chloride (2 times), and the residual gas was washed with 10% sulphuric acid and distilled *in vacuo*. The purification procedure was repeated if an infra-red spectrum showed the acetylenic C–H absorption at 3·0 μ. The product was 1 : 1 : 1-*trifluorobut-2-yne* (39%), b. p. (isoteniscope) (18·0—18·5° (Found: F, 52·7%; *M*, 108. $C_4H_3F_3$ requires F, 52·7%; *M*, 108).

The infra-red spectrum of 1 : 1 : 1-trifluorobut-2-yne was unchanged after treatment of the alkyne with acid catalysts at 110° for 10 hr.

Hydration of 1 : 1 : 1-*Trifluorobut-2-yne*.—The alkyne was substantially unchanged (94%) when heated with mercuric sulphate (1 mol. %) and 10% sulphuric acid at 120° for 8 hr.

In a typical experiment, the butyne (3·14 g., 0·03 mole) was heated with mercuric sulphate (12·0 g., 0·04 mole) and 25% sulphuric acid (8 ml.) at 45—55° for 20 hr. The volatile products were unchanged butyne (0·26 g., 8%), identified spectroscopically, carbon dioxide, and an unknown fraction (0·23 g.) (*M*, 125) shown by spectroscopic examination to contain no carbonyl group. The aqueous and the solid products were extracted with butyl ether, and the ethereal extract was dried (P_2O_5) and distilled, to give a fraction, b. p. 95—98°, which was redistilled, to give 4 : 4 : 4-*trifluorobutan-2-one*, b. p. 95—96° (Found: C, 38·3; H, 4·7%; *M*, 125. $C_4H_5OF_3$ requires C, 38·1; H, 4·0%; *M*, 126). The material of b. p. higher and lower than that shown above was treated with 2 : 4-dinitrophenylhydrazine, to give the 2 : 4-*dinitrophenylhydrazone* (1·68 g.), m. p. 131—132°, of 4 : 4 : 4-trifluorobutan-2-one, since the ketone could not be completely separated from butyl ether by distillation (Found: C, 39·0; H, 3·2; N, 18·3. $C_{10}H_9O_4N_4F_3$ requires C, 39·2; H, 2·9; N, 18·3%). The infra-red spectra of the 2 : 4-dinitrophenylhydrazones of 4 : 4 : 4-trifluorobutan-2-one and 1 : 1 : 1-trifluorobutan-2-one are distinctly different.

The ketone can also be isolated by extraction with ethyl ether, followed by distillation and treatment with phosphoric anhydride. Butyl ether was used in the first experiment so that any 1 : 1 : 1-trifluorobutan-2-one, b. p. 46°, formed could be detected. There is no reason to believe that the breakdown products arise preferentially from 1 : 1 : 1-trifluorobutan-2-one. All fractions were examined by infra-red spectroscopy, and tested for formation of a 2 : 4-dinitrophenylhydrazone.

3-*Chloro*-1 : 1 : 1-*trifluorobut-2-ene*.—Chlorine (4·07 g., 0·057 mole) and 1 : 1 : 1-trifluoro-3-iodobut-2-ene (13·60 g., 0·058 mole) in a sealed Carius tube were kept at −10° for 1 hr., then treated with a slight excess of 10% aqueous potassium hydroxide at 10—20° to remove precipitated iodine halides. The lower layer was added dropwise (3 hr.) to zinc (20 g.) and refluxing ethanol (125 ml.); the ethanol was slowly distilled off during the reaction and added to an excess of ice-water. The lower layer so obtained was dried (P_2O_5) and distilled, to give 3-chloro-1 : 1 : 1-trifluorobut-2-ene (6·2 g., 76%), b. p. 58—60° (Found: *M*, 142. Calc. for $C_4H_4ClF_3$: *M*, 144·5).

1 : 1 : 1-Trifluorobut-2-yne (0·69 g.) failed to react with anhydrous hydrogen chloride (0·26 g.) after 2 days at 140°. Addition of aluminium chloride (0·8 g.) brought about an immediate reaction at room temperature, completed at 95° (10 hr.), to give 1 : 1 : 1-trifluoro-3-chlorobut-2-ene (Found: *M*, 144. Calc. for $C_4H_4ClF_3$: *M*, 144·5) and unchanged butyne (56%). The infra-red spectra of the chlorofluorobutenes made by the two routes were identical.

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*The S_N Mechanism in Aromatic Compounds. Part VII.**

By G. Peter Briner, Joseph Miller, and (in part) M. Liveris and (Miss) P. G. Lutz.

[Reprint Order No. 4735.]

The reactions of *p*-halogenonitrobenzenes with sodium methoxide in absolute methanol have been examined quantitatively, and are discussed as in Part III [Beckwith, Miller, and (in part) Leahy, *J.*, 1952, 3552] for the 1-halogeno-2 : 4-dinitrobenzenes.

By the method reported in Part I (Miller, *Rev. Pure Appl. Chem.*, 1951, **1**, 171) it was shown in Part III (*loc. cit.*) that the relative ease of replacement of halogens in nucleophilic substitutions is the resultant of opposing bond-strength and electronegativity factors, and that the reversal in their relative importance, as in alkyl halides on the one hand and activated aryl halides on the other, takes place between the halogeno- and halogenonitrobenzenes.

In the present work, the rates of attack by OMe^- in absolute methanol on the latter compounds, together with the Arrhenius parameters, are obtained. Bevan (*J.*, 1951, 2340) recently measured the rates of attack by OEt^- in ethanol on these compounds, though he did not discuss the Arrhenius parameters, and regarded his discussion as tentative. The kinetic difficulty with the iodo-compound, due to a side reaction forming free iodine, which he reported, was not encountered in this work. The kinetics for the

Table 1.

Halogen in *p*-$NO_2 \cdot C_6H_4 \cdot$Hal	Temp.	Rate constants, $10^5 k_2$ (l. mole^{-1} sec.$^{-1}$)	Ratio, Cl = 1, at 0°	50°	100°	*E* (cal.)	$\log_{10} B$
Fluorine	0°	(0·626)	—	—	—	—	—
	35·5$_5$	58·7	—	—	—	21,200 ± 100	11·75 ± 0·1
	40·2	104	—	—	—	—	—
	47·3	187·$_5$	—	—	—	—	—
	48·0$_5$	218	703	312	172	—	—
	50	(264)	—	—	—	—	—
	82·0	5,210	—	—	—	—	—
	100	(22,000)	—	—	—	—	—
Chlorine	0	(0·0$_3$890)	—	—	—	—	—
	50	(0·847)	—	—	—	24,050 ± 150	11·2 ± 0·1
	71·0	8·42	—	—	—	—	—
	81·6	23·5	1	1	1	—	—
	100	(128)	—	—	—	—	—
	100·8	137·$_5$	—	—	—	—	—
Bromine	0	(0·0$_3$634)	—	—	—	—	—
	50	(0·716)	—	—	—	24,650 ± 100	11·5 ± 0·1
	82·0	21·8$_5$	—	—	—	—	—
	100	(123)	0·612	0·745	0·961	—	—
	100·1	124	—	—	—	—	—
	120·4	680	—	—	—	—	—
Iodine	0	(0·0$_3$245)	—	—	—	—	—
	50	(0·305)	—	—	—	25,000 ± 200	11·4 ± 0·1
	82·0	11·5$_5$	—	—	—	—	—
	100	(56·4)	—	—	—	—	—
	100·1	56·9	0·275	0·361	0·441	—	—
	120·6	372	—	—	—	—	—
	138·5	1,360	—	—	—	—	—

chloro-compound have been determined less thoroughly by Holleman, de Mooy, and Ter Weel (*Rec. Trav. chim.*, 1916, **35**, 1).

The experimental results, given as Table 1, include, in parentheses, rate constants calculated from the Arrhenius parameters.

* Part VI, *J. Amer. Chem. Soc.*, 1954, **76**, 448.

Discussion of Results.—It is clear from the experimental measurements that the reversal in character from the halogenobenzenes is almost complete with the introduction of the first nitro-group in the *para*-position. Miller (*J.*, 1952, 3550) showed the *o*-nitro-group to be similar; even the *m*-group is effective to a smaller extent, as shown by comparison of *m*-fluoro- and *m*-chloro-nitrobenzene (unpublished work by Liveris, Lutz, and Miller, quoted by Heppolette and Miller, *J. Amer. Chem. Soc.*, 1953, **75**, 4265) and Holleman and de Mooy, *Rec. Trav. chim.*, 1916, **35**, 17).

The differences between the mono- and the dinitro-series are small but in the right

TABLE 2.

Halogen	Halogen ratio at 50°: mononitro-series	Halogen ratio at 50°: dinitro-series	Differences in activation energy (kcal.) mononitro-series	Differences in activation energy (kcal.) dinitro-series
F	312	1200	−3·8	−4·6
Cl	1	1	$-0{\cdot}9_5$	$-1{\cdot}5_5$
Br	$0{\cdot}74_5$	$0{\cdot}62_5$	$-0{\cdot}3_5$	−1·9
I	0·36	0·24	0	0

direction as shown in Table 2. If A is the difference in ionic resonance energy, B the difference in bond strength of the C–Hal bonds, and C the difference in activation energy (all in kcal.), the values being obtained as in Part III, then the equation, $0{\cdot}31B - 0{\cdot}48A = C$, fits well the experimental values relating fluorine, chlorine, and iodine, but does not in this series predict the correct value for bromine, as shown below:

	Halogen in *p*-halogenonitrobenzene: F	Cl	Br	I
C (actual)	−3·8	−0·95	−0·35	0
C (calc.)	−3·8	−0·95	$-1{\cdot}3_5$	0

The main feature, the marked difference between fluorine and the other halogens, is again clearly brought out. There is no obvious explanation for the divergence of bromine, but the forthcoming analysis of the simple halogenobenzenes should throw further light on this point.

The ratio of the electronegativity and the bond-strength factors in the mononitro-series bears a satisfactory relation to that in the dinitro-series, *viz.*, 1·55 as against 1·65: a small but significant increase in the importance of the bond-strength factor is apparent.

As might be expected for simple *para*-substituents the values for $\log_{10} B$ are all very close, the whole range being only 0·55.

Experimental.—The runs were followed as in Part II (*loc. cit.*), but a graphical plot was used for k_2. Runs at each temperature were in duplicate except for those with fluorine at 47·3° and 48·05°. Probable errors in E and $\log_{10} B$ were determined by the method of least squares.

Materials. *p*-Fluoronitrobenzene, prepared from *p*-nitroaniline *via* the diazonium borofluoride in 54% overall yield, had m. p. 26°, b. p. 204—205° (lit.: 26°; 205°). *p*-Chloro-, *p*-bromo-, and *p*-iodo-nitrobenzene were commercial products crystallised to constant m. p. from ethanol and had m. p. 83° (lit., 83°), 124—125° (lit., 125°, 127°), and 172° (lit., 172°), respectively.

As a confirmation of the absence of the side reaction reported by Bevan (*loc. cit.*) several tubes of reaction mixture of the iodo-compound were held at 120·6° for 4 days. No free iodine could be detected.

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The Kinetics of Aromatic Halogen Substitution. Part X. The Intermediates involved in Halogenation in Acetic Acid Solution.*

By P. W. Robertson.

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The influence of electrolytes on halogenation by solutions of halogen in acetic acid solution indicates that positive halogen ions and halogen acetates play no part in the reactions. Electrolytes appear to act by an activity effect promoting the anionisation of a halogen atom from the intermediate, ArH,X_2. The differences between mechanisms involving X_2 and X^+ are discussed.† Measurements of the influence of added hydrogen bromide on the rate of bromination of mesitylene show that the termolecular reaction, $A + 2Br_2$, is changed with excess of hydrogen bromide into a bimolecular reaction, $A + Br_2$, catalysed by hydrogen bromide.

Throughout the present series of investigations, and in the parallel series on halogen addition, we have interpreted the experimental evidence as indicating that the initial halogen attack is by a neutral halogen molecule. In certain kinetic studies the possible participation of other entities has been examined in detail. Bartlett and Tarbell (*J. Amer. Chem. Soc.*, 1936, **58**, 466), for instance, have shown that, in the action of bromine on stilbene in methyl-alcoholic solution, the compound BrOMe plays no part. Again, Bradfield and Brynmor Jones (*Trans. Faraday Soc.*, 1941, **37**, 734) and Bradfield, Davies, and Long (*J.*, 1949, 1389) concluded that, in the bromination of phenol ethers in acetic acid solution containing 25% of water, the electrophilic reagent is the bromine molecule, Br_2, or Br_4, rather than such possible intermediaries as BrOH, BrOAc, or " positive " bromine. Similarly for chlorination it was concluded by Bradfield and Brynmor Jones (*Trans. Faraday Soc.*, 1941, **37**, 726) that no mechanism other than the direct interaction between chlorine and the phenol ether comes into play. Our own studies, more particularly with regard to the effect of electrolytes on the rates (Parts I, II, and V, *J.*, 1943, 276, 279; 1949, 294), are in agreement with this interpretation. Such a view, however, has not been universally accepted. For instance, Baker (" Hyperconjugation," Oxford Univ. Press, 1952, p. 52), discussing our results, writes " . . . in halogenation many different potential sources of Cl^+ may be acting simultaneously, and until it is possible to study both comparative rate and orientation data under experimental conditions when only a single halogenating entity is operative, no reliable conclusions can be drawn." With reference to bromination in acetic and aqueous acetic acid it is stated by Ingold (" Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 289): " In these media it seems certain that molecular bromine is one of the effective bromine carriers; but there are complications that have not been fully elucidated; and it is not clear what part, if any, the expected carrier acetyl hypobromite plays in these brominations." Certain results, hitherto unpublished, which are of diagnostic value with regard to the mechanisms of bromination, are now presented, together with a formal review of the evidence that has a bearing on the nature of both chlorination and bromination.

In chlorination the rates are not disturbed by the concurrence of higher-order reactions as in bromination, nor is there intervention, to any appreciable extent, of the subsidiary reaction, $Cl_2 + HCl \rightleftharpoons HCl_3$. Added electrolytes show a small positive catalysis, which is in the order of their conductivities, $HClO_4 > LiCl \approx HCl > NaOAc$, becoming very slight for the last compound. This is considered (Part V, *loc. cit.*) to be a salt (activity) effect, such as is found in other halogenation reactions, addition as well as substitution, in acetic acid solution. These activity effects become less in aqueous acetic acid in accordance with theoretical expectation.

The slight influence of Cl^- ions (*i.e.*, as added LiCl or HCl) shows that a mechanism

* Part IX, *J.*, 1953, 782. † In this paper, except where otherwise specified, the symbol X^+ is used to imply either the free ion or the form in which it is covalently attached to a solvent molecule HOAc, or possibly H_2O in the aqueous solutions.

involving Cl^+ ions is not possible. The equilibrium, $Cl^+ + Cl^- \rightleftharpoons Cl_2$, is displaced almost completely to the right, so that the concentration of Cl^+ ions in the reacting mixtures must be virtually zero. The possibility that there might be initially an exceedingly small concentration of very highly reactive Cl^+ ions is also excluded, since in that case the HCl formed in the substitution would immediately destroy the reactive reagent, and the initial bimolecular rate would fall off rapidly. Actually the bimolecular coefficients gradually increase owing to the catalytic effect of the HCl formed in the reaction.

It has also been suggested that chlorine acetate may be an intermediate in the reactions, either as such or as the protonated molecule. In the first instance the expected mode of formation would be represented :

$$Cl_2 + HOAc \rightleftharpoons ClOAc + H^+ + Cl^- \rightleftharpoons HCl + ClOAc$$

As the chlorine is in very large excess over the chlorine acetate, then, the kinetic form being $-d[Cl_2]/dt = k[ArH][Cl_2]$, this equilibrium would have to be established rapidly. The addition to the solution of HCl (or of H^+ or Cl^- ions) would cause displacement to the left and so reduce the rate of reaction. Since HCl does not have this effect, it follows that chlorine acetate is not an essential intermediate.

A second possible route is through the rapidly established equilibrium

$$Cl_2 + HOAc \rightleftharpoons ClOAcH^+ + Cl^-$$

Again, a reaction proceeding by this route, and having the kinetic form, $-d[Cl_2]/dt = k[ArH][Cl_2]$, would be impeded by Cl^- ions, as is contrary to the facts. Hence $ClOAcH^+$, like Cl^+ and ClOAc, cannot be regarded as an essential intermediate.

Such theoretical conclusions have now received direct experimental confirmation, since recently chlorine acetate has been prepared in acetic acid solution, and its kinetics have been investigated by de la Mare, Ketley, and Vernon (*Research*, 1953, **6**, 12*S*). Its solutions are immediately decomposed by Cl^- ions, and in its reactions it is " enormously catalysed by mineral acids." It thus differs markedly from a solution of chlorine, for which acids and bases (NaOAc) are not specific, and Cl^- ions have merely a slight positive effect.

In general, similar arguments can be used to prove that neither Br^+ ions nor bromine acetate can be intermediates in the bromination by bromine in acetic acid solution. Although no kinetic experiments on bromine acetate have been reported, it is very probable that it would react in a similar manner to chlorine acetate, and show strong acid catalysis. This is not a characteristic of aromatic bromination; the influence of added electrolytes is relatively small, and, as for chlorination, in the order of their relative conductivities, *viz.*, $HClO_4$ ($\approx LiClO_4$) > LiCl > NaOAc.

Whereas in chlorination the effect of Cl^- ions is in accord with the non-intervention of chlorine acetate in the reactions, their effect in bromination offers less certain evidence, since with bromine acetate, or Br^+ ions, they would form bromine chloride, which is a more reactive reagent than bromine. Such a possible ambiguity in interpretation may be avoided by the study of the effect of Br^- ions on the reaction. Accordingly, we report data on the bromination of mesitylene in the presence of varying amounts of HBr. The investigation is confined to the early stages of the reaction, and, in accordance with previous practice, the times at $x = 10\%$ bromine absorption are taken as a measure of the relative initial rates (Figs. 1, 2).

The interpretation of these experimental results is that added HBr gradually converts the third-order bromination ($A + 2Br_2$) into a reaction of the second order ($A + Br_2$). This is in part due to the removal of the bromine as unreactive HBr_3, thus eliminating the third-order reaction, which is favoured by a high concentration of bromine, but more especially to the establishment of a second-order reaction catalysed by hydrogen bromide. Under the conditions when the relative rates become approximately constant with increasing amounts of HBr, the equilibrium in the reaction, $HBr + Br_2 \rightleftharpoons HBr_3$, is shifted largely to the right, so that the rate expression becomes $\sim k[A][Br_2][HBr]$. This, however, does not mean that the HBr is taking an integral part in the reaction, one molecule

being involved for each molecule of bromine, but that its catalytic effect happens to be equivalent per molecule to one molecule of bromine under the experimental conditions. The rate expression is more correctly $(k + k'[HBr])[A][Br_2]$, and there is also a contribution from the reaction whose rate is given by $(k + k''[HBr_3])[A][Br_2]$.

It is clear that hydrogen bromide acts as a positive catalyst. This result, together with the facts that the reaction is not strongly acid-catalysed and that its rate is not reduced by added sodium acetate, indicate that neither bromine acetate nor Br^+ ions can be intermediates in aromatic bromination in pure acetic acid. A similar conclusion was reached by Bradfield, Davies, and Long (*loc. cit.*) for 25% aqueous acetic acid, and our kinetic measurements in this mixed solvent have been carried out within the concentration range containing 10—20% of water.

FIG. 1. *Mesitylene* M/80 + *bromine* M/80.

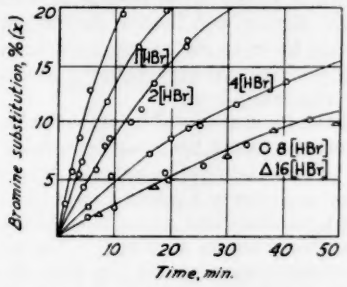
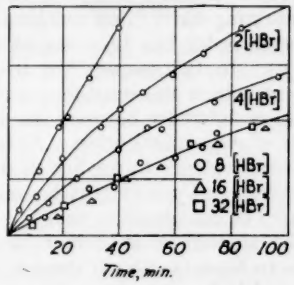


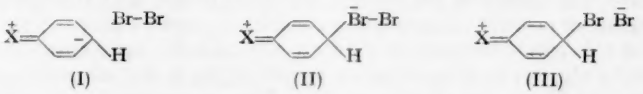
FIG. 2. *Mesitylene* M/160 + *bromine* M/160.



Not only is the effect of catalysts in halogenation not in accord with the intervention of halogen acetates, but it is in agreement with a mechanism according to which there is a direct electrophilic attack by the halogen molecule on the organic compound. For example, the reaction with bromine would proceed :

$$ArH + Br_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ArH,Br_2 \xrightarrow{k_3} Br^- + ArHBr^+ \xrightarrow{k_4} ArBr + H^+$$

The structures (I), (II), and (III) are among those that contribute to the intermediate.



The final stage (k_4) is too rapid to affect the rate * which consequently becomes equal to $(k_1/k_2)k_3[ArH][Br_2]$. The magnitude of k_3 will be increased by any factor that promotes the anionisation of the bromine, *viz.*, (*a*) added water (solvating effect), (*b*) electrolytes (activity effect), (*c*) iodine, which acts as IBr and forms the IBr_2^- ion, and (*d*) increase in the concentration of the bromine, which promotes the formation of Br_3^- ions.†

When the environmental factors are kept constant, and a comparison is made in a series of compounds PhX, where the group X has $+T$ characteristics, the electronic flow from X influences the rate by its effect on k_1/k_2. The impulse is relayed from atom to atom, as indicated in the resonance structures (I—III), and finally assists in the anionisation of the bromine. A change in the group X thus involves a change, in the same sense, in both k_1/k_2 and k_3. In this way may be explained the large spread in rates observed for such reactions, the relative values varying for instance from 10^{18} for $Ph{\cdot}NMe_2$ to unity for

* This is probable since sodium acetate, a base in acetic acid, causes little acceleration. Melander (*Arkiv Kemi*, 1950, **2**, 213) by an independent method proved that the removal of the proton was not a rate-determining stage in aromatic bromination.

† The effects represented by *a* and *b* are in competition with *d*, and tend to reduce the reaction order, as is found experimentally. Consequently, in acetic acid solution the third-order reaction would appear to proceed, $A + Br_2 \underset{}{\overset{Br_2}{\rightleftharpoons}} A,Br_2 \longrightarrow$ Products, in preference to the alternative scheme, $A + Br_2 \rightleftharpoons Br_2 + A,Br_2 \longrightarrow$ products, which shows similar kinetics (Part I, *loc. cit.*; Part IV, *J.*, 1948, 100).

PhH (Part IX). Such a spread in rate becomes greatly reduced in bromination *via* the Br^+ ion, which proceeds according to the scheme :

$$ArH + Br^+ \xrightarrow{k} ArHBr^+ \xrightarrow{Rapid} Products$$

As an example of such a difference in rate-ratio may be cited the cases of toluene and benzene, the value for Br_2 being 470 (Berliner and Berliner, *J. Amer. Chem. Soc.*, 1949, **71**, 1195), and for the Br^+ ion 20 (de la Mare, Ketley, and Vernon, *loc. cit.*).

When, however, for a compound PhX, where X has $+T$, $-I$ characteristics, the rate is less than the rate for benzene, then the inductive effect has a relatively greater influence on the rate than the tautomeric effect. Under these conditions the spread in rate, with reference to benzene, may become greater for the ionic than for the molecular mechanism. In an extreme case the rate relative to that of benzene may be even reversed. Thus fluorobenzene reacts less rapidly than benzene with acidified hypochlorous acid in acetic acid containing water (ionic mechanism; de la Mare, Ketley, and Vernon, *loc. cit.*), whereas the reverse order has been found for chlorination by chlorine in aqueous acetic acid (Part IV). In this respect the reagent yielding positive chlorine behaves similarly to nitric acid, which on nitration reacts through the nitronium ion.

Another difference between the molecular and the ionic mode of bromination is in the amounts of *meta*-substitution. Although direct measurements have not been made, there is sufficient evidence to predict their magnitude. From the relative rates of bromination of mesitylene and pentamethylbenzene the partial rate factor in a position *meta* to a methyl group may be calculated to be 3·6. This value with toluene–benzene ratio for bromination gives the amount of *m*-bromotoluene formed in this reaction as 0·26%. On nitration (toluene to benzene, 25 : 1) there is 3·2% of *meta*-substitution, and it has been shown by Brown and Nelson (*J. Amer. Chem. Soc.*, 1953, **75**, 6292) that with decrease in the rate-ratio of toluene to benzene with different reagents the *meta*-substitution of toluene increases. Consequently, on bromination with the Br^+ ion (toluene to benzene, 20 : 1) the amount of *m*-bromotoluene formed must be more than 3·2%, *i.e.*, a considerably greater amount than that produced by molecular bromination.

These differences are characteristic and considerable, and strengthen the view that the participation of the ionic mechanism in halogenation by solutions of chlorine or bromine, if any at all, must be slight. The kinetic evidence based on the effect of electrolytes is, however, decisive, and neither in bromination by bromine nor in chlorination by chlorine can halogen acetate or positive halogen ion be considered to play a part. Thus, contrary to Baker's opinion (*op. cit.*), halogenation data are available for constitutional studies. In chlorination, certainly, our own experiments, as well as the earlier measurements of Orton, Bradfield, Brynmor Jones, and their co-workers, have been carried out under conditions where only a single halogen entity is operative. In bromination, on the other hand, reactions of different kinetic order may proceed simultaneously, but comparative measurements with a series of compounds have always been carried out under conditions in which the kinetic forms were identical. When comparisons have been possible with the corresponding rates of chlorination, similar rate-sequences have been observed, and even small differences in rate have been reproduced (see, *e.g.*, Orton, Bradfield, and Brynmor Jones, *J.*, 1929, 2810).

Experimental.—The experimental technique is as described in previous communications. The figures in the text are from measurements by (the late) R. M. Dixon. It was shown by I. J. Lambourne that pentamethylbenzene behaved in a similar manner to mesitylene, giving rates of bromination which became constant with increasing amounts of added hydrogen bromide. The rate-ratio for the two compounds with bromine (reactants M/80 and hydrogen bromide M/10) was 4·7, the previously found value (Part II, *loc. cit.*) for the reaction without hydrogen bromide being 4·3. This value was used for the calculation of the partial rate factor for a *meta*-position due to one methyl group in pentamethylbenzene, and consequently also in toluene, *viz.*, $\sqrt{3 \times 4{\cdot}3} = 3{\cdot}6$.

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The Nitration and Hydroxylation of Phenetole, Phenyl n-*Propyl Ether, and Acetophenone by Pernitrous Acid.*

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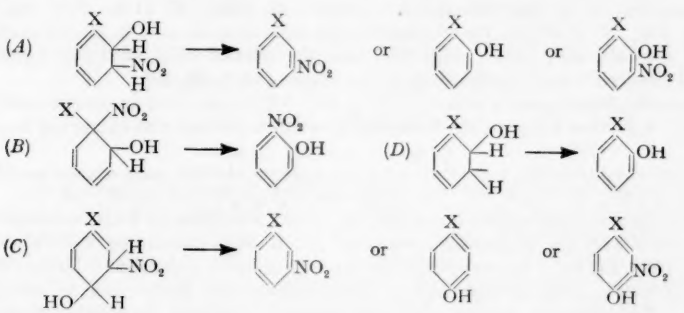
Reaction of pernitrous acid (cf. Halfpenny and Robinson, *J.*, 1952, 928, 939) with the compounds mentioned in the title leads to nitration and hydroxylation, the nature of the side-chain influencing the susceptibility of the nucleus and the nature of the products. The hydroxy- and mononitro-derivatives conform to the scheme previously advanced, but dinitro-compounds are formed to a considerable extent from the two ethers.

Halfpenny and Robinson (*J.*, 1952, 928, 939) reported the use of pernitrous acid as a nitrating and hydroxylating agent for anisole. We now describe its reactions with phenetole, phenyl *n*-propyl ether, and acetophenone. Halfpenny and Robinson (*loc. cit.*) considered the main products to arise by homolytic fission of pernitrous acid: $HO{\cdot}O{\cdot}NO \longrightarrow HO + NO_2$. The hydroxyl radical then enters the nucleus, preferentially in the *ortho*- or *para*-position to form an aryl radical. This reacts with nitrogen dioxide to give an unstable molecular species which breaks down with the elimination of water, nitrous acid, or hydrogen. The expected products from a monosubstituted benzene are then as in (*A*)—(*C*).

It was also pointed out that purely hydroxylated products can result from a more direct process (*D*) in which there is no intervention of nitrogen dioxide.



Our results are tabulated below, along with those already reported for anisole, the yields being those from the same weight (2000 g.) of each starting material.

Starting material, PhR	R·C$_6$H$_3$(NO$_2$)·OH 4 : 2 : 1- (g.)	6 : 2 : 1- (g.)	6 : 2 : 4 : 1- R·C$_6$H$_2$(NO$_2$)$_2$·OH (g.)	*o*-R·C$_6$H$_4$·OH (g.)	Other products
Ph·OMe	7·6	0·4	—	—	Ph·OH (29·6 g.), *o*-NO$_2$·C$_6$H$_4$·OH (7·9 g.)
Ph·OEt	—	8·25	2·6	8·55	
Ph·OPr	—	—	2·0	—	
Ph·COMe ...	—	3·65	—	2·5	*m*-NO$_2$·C$_6$H$_4$·COMe (15·6 g.), Ph·CO$_2$H (0·08 g.)

When the side-chain is longer than methoxyl it is not replaced by hydroxyl. There is a slight conversion of acetyl into carboxyl, by either substitution of the methyl by an hydroxyl group or oxidation: apart from this, the attack is restricted to the benzene nucleus. With increasing molecular weight, compounds 4 : 2 : 1-R·C$_6$H$_3$(NO$_2$)·OH are replaced, in the cases of phenetole and acetophenone, by derivatives of the 6 : 2 : 1-type. Apparently this does not happen with phenyl *n*-propyl ether; here the only compound identified was 2 : 4-dinitro-6-propoxyphenol, corresponding to the dinitro-derivative

obtained as minor product from phenetole. Dinitration increases concurrently with the length of the side-chain. The high yield of *m*-nitroacetophenone is a notable feature.

In light of the views previously advanced, *o*-R·C_6H_4·OH arise from reaction (*A*) or (*D*), 6 : 2 : 1-R·$C_6H_3(NO_2)$·OH from reaction (*A*), and *m*-nitroacetophenone from reaction (*C*). Where there is simple hydroxylation, it is found, as predicted, in the *ortho*-position with respect to the original substituent; where there is both hydroxylation and nitration the former occurs in the *ortho*- and the latter in the *meta*-position. The two dinitro-compounds produced are identical in form, but that they spring from further nitration of mononitro-compounds is doubtful since we have not been able to find evidence of the presence of 2-nitro-6-propoxyphenol. The nature of the dinitro-compounds lends support to our opinion that the reactions involved are not ionic.

Diphenyl ether gave so little evidence of attack by pernitrous acid as to discourage an attempt to work up the products. This result is in line with the marked effect of the mass of the aliphatic side-chain.

Experimental

The aromatic compound (100 g.) was agitated with 5% hydrogen peroxide solution (100 c.c.), 3N-hydrochloric acid (5 c.c.), and water (250 c.c.), and 5% sodium nitrite solution (150 c.c.) was added during about 30 min. at room temperature (slightly higher for acetophenone). Only the organic liquid layer was examined.

Phenetole.—After the addition of the nitrite, the organic layer appeared bright orange, the aqueous layer paler. Organic material from 20 experiments was extracted with 8% aqueous sodium hydroxide. This dark red solution was shaken several times with ether to remove unchanged phenetole, then acidified (becoming yellow) and extracted with ether and finally ethyl acetate. The two extracts, after drying (Na_2SO_4) and removal of solvents, left a brown viscous liquid (21·0 g.) from which crystals separated (2·4 g.). These recrystallised from alcohol as yellow needles, m. p. 155° (Found : C, 42·65; H, 3·85; N, 11·8. Calc. for $C_8H_8O_6N_2$: C, 42·1; H, 3·5; N, 12·3%). De-ethylation with hydrobromic acid in glacial acetic acid gave pale yellow crystals, m. p. 164°, suggesting that the original compound was 6-ethoxy-2 : 4-dinitrophenol (Reverdin and Fürstenberg, *J. pr. Chem.*, 1913, **88**, 327).

The remaining liquid gave a yellow oil, b. p. 65—70°/3 mm., and an orange solid, b. p. 120—130°/3 mm. A further 0·2 g. of the 6-ethoxy-2 : 4-dinitrophenol was extracted from the brown residue.

The orange solid (8·25 g.), recrystallised from aqueous alcohol, gave orange needles, m. p. 79° (Found : C, 51·95; H, 5·15; N, 7·5. Calc. for $C_8H_9O_4N$: C, 52·25; H, 4·9; N, 7·65%). De-ethylation as above gave yellow needles, m. p. 82°, identified as 3-nitrocatechol by a mixed m. p. (82—84°) with the authentic compound (m. p. 86°) (Foglesong and Newell, *J. Amer. Chem. Soc.*, 1930, **52**, 834), the red-purple colour with sodium hydroxide solution (Weselsky and Benedikt, *Monatsh.*, 1882, **3**, 386), and the green colour with ferric chloride solution (catechol derivative). This evidence suggests that the original compound is probably 6-ethoxy-2-nitrophenol. It is appreciably volatile in steam.

The yellow oil (8·55 g.) was shown to be principally 2-ethoxyphenol by de-ethylation to almost colourless crystals (from hydrochloric acid) shown to be catechol by a mixed m. p. determination, the green colour with ferric chloride solution, and formation of the dibenzoyl derivative, m. p. 85°.

Phenyl n-*Propyl Ether.*—After the addition of nitrite the organic layer appeared lemon-yellow, the aqueous layer much paler. The organic material from 20 experiments, worked up as above, gave, by acidification of the alkaline extract, a light brown precipitate (1·9 g.). Recrystallisation from alcohol yielded yellow crystals, m. p. 88° (Found : C, 45·5; H, 4·65; N, 13·4. Calc. for $C_9H_{10}O_6N_2$: C, 44·6; H, 4·1; N, 11·6%). Attempts to depropylate the substance were unsuccessful, but it gave absorption curves, in both the ultra-violet and the visible range, which were so similar to those of the 6-ethoxy-2 : 4-dinitrophenol as to leave little doubt that it was 2 : 4-dinitro-6-propoxyphenol. The remaining aqueous solution was extracted and the products were distilled as above, to give a yellow oil (0·4 g.), b. p. 60—65°/5 mm., and a viscous orange liquid (1·0 g.), b. p. 130°/5 mm. A further 0·1 g. of the solid, m. p. 88°, was obtained from the residue. Attempts at depropylation of both fractions failed and the compounds have not been identified. Absorption spectra did not however indicate that either contained 2-nitro-6-propoxyphenol.

Acetophenone.—To prevent solidification the reaction was carried out at 20—25°. On

addition of the sodium nitrite the organic layer became dark amber and the aqueous layer lemon-yellow. The organic material from twenty experiments was worked up as above, giving from the extractions, a brown oil (7·7 g.). Steam-distillation produced a pale yellow distillate which was extracted with ether. After drying (Na_2SO_4) and removal of the ether, distillation under reduced pressure gave a pale brown oil (2·5 g.), and sublimation of the residue yielded an almost colourless solid (0·08 g.) and left a trace of tar. The oil was identified as *o*-hydroxyacetophenone by its semicarbazone, m. p. 210°, and its oxime, m. p. 116°. The solid, after recrystallisation from hot water, melted at 121° and was proved to be benzoic acid by the ferric chloride test, and a mixed melting point determination.

The residue from the steam-distillation was extracted with ether, and the solution dried (Na_2SO_4). Removal of the solvent left a brown, viscous liquid (4·1 g.) which, on distillation at 4 mm., gave a pale yellow solid (3·65 g.), m. p. 90° after recrystallisation from dilute aqueous acetic acid. It was, probably, 2-hydroxy-3-nitroacetophenone. Unfortunately we have been unable to prepare the oxime, the only derivative mentioned in the literature. This was made (Lindemann and Romanoff, *J. pr. Chem.*, 1929, **122**, 214) by nitrating the oxime of *o*-hydroxyacetophenone and the ketone was obtained from it. We have made the 2 : 4-dinitrophenylhydrazone, m. p. 242°, but neither it nor the corresponding amino-compound appears in the literature. Our ketone is, however, like that of Lindemann and Romanoff in m. p. and ready solubility in cold benzene, acetic acid, and hot water.

The acetophenone, after removal of the phenols, washing with water, and drying (Na_2SO_4), was evaporated under reduced pressure, to leave a brown solid (16·2 g.). Distilled at 3 mm. pressure, this gave a pale yellow solid (15·6 g.) which, after crystallisation from alcohol, was almost colourless and had m. p. 81°. It was shown to be *m*-nitroacetophenone by means of its oxime, m. p. 130°, and phenylhydrazone, m. p. 128°.

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Perfluoroalkyl Grignard and Grignard-type Reagents. Part IV. Trifluoromethylmagnesium Iodide.†*

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Trifluoromethylmagnesium iodide is prepared from trifluoroiodomethane only with difficulty. Neutral-molecule Lewis bases are the best solvents, and temperatures of −30° to −10° should be used. Fluoroform and polytetrafluoroethylene are produced by decomposition of the Grignard compound and the mechanism of formation of these compounds is discussed. The conversion of $CF_3{\cdot}MgI$ into CHF_3, $CF_3{\cdot}CO_2H$, or $CF_3{\cdot}CH_2{\cdot}CH_2{\cdot}OH$, and into the ketones $CF_3{\cdot}CO{\cdot}R$ (R = Me, Et, Pr^n, CH_2F, CHF_2, $CF_3{\cdot}CH_2$, CF_3, or C_3F_7) is described.

TRIFLUOROMETHYLMAGNESIUM IODIDE was the first perfluoroalkylmagnesium iodide to be prepared (Haszeldine, *Nature*, 1951, **167**, 139; **168**, 1028; Abs. Amer. Chem. Soc. Meetings, Sept. 1951, 6K; Sept. 1952, 13K), but it was soon found that the experimental results were difficult to reproduce and that a variety of factors were influencing the formation of the Grignard compound. Pentafluoroiodoethane also yielded a magnesium derivative, but the results were again difficult to reproduce precisely, although (as will be shown in a later paper) for a different reason. Heptafluoroiodopropane reacts with magnesium much more smoothly than does trifluoroiodomethane, and the results can readily be duplicated; for this reason heptafluoroiodopropane, which is typical of the iodo-compounds $CF_3{\cdot}[CF_2]_n{\cdot}I$ where $n > 1$, was used to determine the conditions necessary for the formation of a perfluoroalkyl Grignard compound in optimum yield (Part I, *J.*, 1952, 3423). The present communication reports the early results with trifluoromethylmagnesium iodide.

The conditions which affect the formation of trifluoromethylmagnesium iodide are, in decreasing order of importance, the initiation of the reaction, the temperature, the

* Part III, *J.*, 1953, 3607. † Parts of this paper have been presented at the Amer. Chem. Soc. Meetings, September 1951 (New York) and September 1952 (Atlantic City).

solvent, and the dilution of the fluoro-iodide in the solvent. Pure magnesium and completely anhydrous conditions are essential. The main difficulty in the preparation of the Grignard compound is to start the reaction with magnesium. Heptafluoroiodopropane reacts with magnesium approximately one thousand times as readily as does trifluoroiodomethane, particularly at the low temperatures which have to be used to prevent the extensive decomposition of the Grignard compound once formed. For this reason other methods, to be described later, for the preparation of a trifluoromethyl Grignard or Grignard-type reagent have been developed, notably exchange reactions of trifluoroiodomethane with aryl Grignard reagents or with alkyl-lithium compounds. The methods used to initiate reaction between trifluoroiodomethane and magnesium are described in the Experimental section, but it must be emphasised that there is often little or no formation of the Grignard compound under conditions apparently identical with those which, in a separate experiment, gave a relatively high yield. The amount of trifluoromethylmagnesium iodide (maximum yield 45%) available for a particular reaction should therefore be determined from an aliquot of the solution to be used.

The solvent plays an important part. Trifluoroiodomethane does not react with magnesium when benzene, *cyclo*hexane, or perfluoromethyl*cyclo*hexane is solvent. A basic solvent, in the Lewis sense, is required, and the reason for this is now clear. A solvent B, which contains an atom or atoms (*e.g.*, O, N) containing lone pairs of electrons, has been shown to form a molecular compound of the type (RI),B with a fully fluorinated iodo-alkane, RI (Haszeldine, *J.*, 1953, 2622); the iodo-compound is thus a neutral-molecule Lewis acid, and the complex is of the donor–acceptor type, the donated electron in the structure $\psi[B^+–(RI)^-]$ being derived from the lone pair of electrons in B. Thus, although in a non-polar solvent heterolytic fission of the carbon–iodine bond is difficult to achieve, in a basic solvent the carbon–iodine bond probably approaches more to that in an unsubstituted alkyl iodide such as methyl iodide in character, and reactions which involve ionic intermediates are facilitated. On this basis one can interpret the facts that the preparation of heptafluoropropylmagnesium iodide is possible in ethyl ether and triethylamine, but impossible in the non-basic solvents $N(C_3F_7)_3$ or $(C_4F_9)_2O$, and that the yield of the Grignard compound is increased if the more basic tetrahydropyran is used (Part I). Trifluoroiodomethane is similarly more reactive towards magnesium in tetrahydropyran than in ethyl ether. A basic solvent also doubtless stabilises the Grignard reagent by co-ordination and prevents coating effects on the magnesium.

Low reaction temperatures give a higher yield of trifluoromethylmagnesium iodide, since thermal decomposition of the Grignard compound is reduced. The improved yield is counteracted, from the point of view of convenience, by the decreased rate of reaction of the fluoro-iodide with the magnesium, and complete reaction of trifluoroiodomethane cannot be achieved. In cases where the second component can be added during the formation of trifluoromethylmagnesium iodide, however, a reaction temperature *ca.* 0° can be used, since the Grignard compound is removed by reaction as soon as it is formed, with only slight thermal decomposition.

Hexafluoroethane is not a by-product from the formation of the Grignard compound (cf. the isolation of perfluorohexane when heptafluoroiodopropane reacts with magnesium; Part I). Two main by-products have been detected: fluoroform, and tetrafluoroethylene, which is obtained as a polymer. The formation of fluoroform is readily explained on the basis of a trifluoromethyl anion:

$$CF_3{\cdot}MgI \longrightarrow CF_3^- + \overset{+}{M}gI;\ CF_3^- + \text{solvent} \longrightarrow CHF_3$$

That the polymer arises mainly from tetrafluoroethylene is shown by pyrolysis studies. Tetrafluoroethylene formation can be visualised as

$$2CF_3^- \longrightarrow C_2F_4 + 2F^-$$

i.e., elimination of fluoride ion from two fluorocarbanions. The formation of hexafluoropropene from heptafluoropropylmagnesium iodide is believed to involve

$$CF_3{-}\underset{\displaystyle F}{CF}{-}CF_2^- \longrightarrow CF_3{-}CF{=}CF_2 + F^-$$

Alternatively, trifluoromethylmagnesium iodide may undergo halogen exchange with trifluoroiodomethane to give difluorodi-iodomethane :

$$CF_3{\cdot}MgI + CF_3I \longrightarrow CF_3{\cdot}MgF + CF_2I_2$$

$$2CF_2I_2 \xrightarrow{Mg} C_2F_4$$

The formation of trifluoromethylmagnesium fluoride would account for the magnesium fluoride always produced during reactions of the Grignard compound. The polymerisation of tetrafluoroethylene cannot involve a simple ionic mechanism,

$$CF_3^- + C_2F_4 \longrightarrow CF_3{\cdot}CF_2{\cdot}CF_2^- \xrightarrow{C_2F_4} \text{etc.}$$

since compounds such as C_3HF_7, C_5HF_9, etc., would be expected in the reaction products. As suggested in Part I, however, anionic polymerisation by the Grignard compound is feasible :

$$CF_3^- \overset{+}{M}gI \xrightarrow{C_2F_4} [CF_3{\cdot}CF_2{\cdot}CF_2]^- \overset{+}{M}gI \xrightarrow{C_2F_4} CF_3{\cdot}[CF_2{\cdot}CF_2]_n^- \overset{+}{M}gI$$

The decomposition of trifluoromethylmagnesium iodide into a trifluoromethyl radical would readily explain the isolation of fluoroform, but not the formation of polytetrafluoroethylene.

When trifluoromethylmagnesium iodide undergoes rapid thermal decomposition, fluoroform, polytetrafluoroethylene, and small amounts of tetrafluoroethylene monomer are produced.

Although difficult to prepare, trifluoromethylmagnesium iodide is a valuable reagent in synthetic fluorine chemistry, and its value will be increased once some way has been found to improve its preparation and to increase its thermal stability (*e.g.*, by formation of a co-ordination compound). Compounds which contain active hydrogen react immediately to yield fluoroform. The reaction with carbon dioxide gives a high yield of trifluoroacetic acid, thus providing an alternative to the oxidation route described earlier (*J.*, 1950, 3037; *Nature*, 1950, **166**, 192). The reaction with carbon dioxide proceeds smoothly at temperatures as low as −60°. Several unsuccessful attempts were made to cause methyl iodide to react with trifluoromethylmagnesium iodide, and it appears that the Grignard compound is anomalous in this respect.

Other reactions carried out with trifluoromethylmagnesium iodide are summarised by the following equations :

$$CH_3{\cdot}CN \longrightarrow CF_3{\cdot}CO{\cdot}CH_3\ (38\%);\quad CF_3{\cdot}CN \longrightarrow CF_3{\cdot}CO{\cdot}CF_3\ (33\%)$$

$$\overset{\frown}{CH_2{\cdot}CH_2O} \longrightarrow CF_3{\cdot}CH_2{\cdot}CH_2{\cdot}OH\ (57\%)\ [\longrightarrow CF_3{\cdot}CH_2{\cdot}CO_2H \longrightarrow CF_3{\cdot}CH_2{\cdot}COCl]$$

$$CH_3{\cdot}COCl \longrightarrow CF_3{\cdot}CO{\cdot}CH_3\ (59\%);\quad Et{\cdot}COCl \longrightarrow CF_3{\cdot}COEt\ (47\%)$$

$$Pr{\cdot}COCl \longrightarrow CF_3{\cdot}COPr\ (51\%);\quad CF_3{\cdot}CH_2{\cdot}COCl \longrightarrow CF_3{\cdot}CO{\cdot}CH_2{\cdot}CF_3\ (37\%)$$

$$CH_2F{\cdot}COCl \longrightarrow CF_3{\cdot}CO{\cdot}CH_2F\ (15\%);\quad CHF_2{\cdot}COCl \longrightarrow CF_3{\cdot}CO{\cdot}CHF_2\ (59\%)$$

$$CF_3{\cdot}COCl \longrightarrow CF_3{\cdot}CO{\cdot}CF_3\ (49\%);\quad C_3H_7{\cdot}COCl \longrightarrow CF_3{\cdot}CO{\cdot}C_3H_7\ (43\%)$$

The reactions of nitriles and of ethylene oxide proceed normally, and the reactions with acyl halides give satisfactory yields of the ketones. It is clear that as techniques for their manipulation are developed, the perfluoroalkyl Grignard compounds will be more used.

Experimental

Trifluoroiodomethane was prepared from carbon tetraiodide and iodine pentafluoride (*J.*, 1948, 2188) or, in the later studies, from silver trifluoroacetate and iodine (*J.*, 1951, 584); it was thoroughly dried and stored *in vacuo*. Sealed Pyrex 50—500-ml. tubes were used for the experiments, and where possible the reactants were transferred *in vacuo*. Stringent precautions were taken to use anhydrous reactants and to exclude moisture, oxygen, and carbon dioxide. Spectroscopically pure magnesium was used.

Conditions affecting Formation of Trifluoromethylmagnesium Iodide.—The effects observed in the early experiments were similar to those reported for heptafluoropropylmagnesium iodide (Part I). The yield of the Grignard reagent was determined (after removal of excess of magnesium, used in all experiments) (*a*) by hydrolysis with water, 5N-hydrochloric acid, or occasionally ammonium chloride, or (*b*) by carboxylation with carbon dioxide as solid or gas,

or addition of the Grignard solution to a mixture of solid carbon dioxide and the solvent. Trifluoroacetic acid was isolated as its sodium salt and for estimation was converted into the amide, or more simply into the silver salt. Handling losses on the scale used were 10—20%, determined from blank experiments.

(a) *Magnesium and initiation.* Although extensive reaction occurred once Grignard formation had been initiated, the yield of trifluoromethylmagnesium iodide ultimately available for reaction was very low unless pure magnesium was used (cf. Part I). For best results the magnesium was freshly cut from a magnesium rod, preferably covered by anhydrous ether and in the absence of air. With such magnesium the formation of trifluoromethylmagnesium iodide was seldom spontaneous, and various devices, not always effective, were used to bring about reactions: Iodine (10—20% of the amount required to form magnesium iodide) was heated (150°) with the magnesium in absence of solvent, and the resultant mixture was used immediately. Alternatively, the magnesium was pretreated with methyl or ethyl bromide or iodide in ether for several minutes until the formation of alkylmagnesium halide was proceeding smoothly; most of the Grignard solution was then drained off and the residual magnesium was sealed with fresh solvent and trifluoroiodomethane. If reaction failed to start at 0—15°, the mixture was heated to 40—50° to initiate the reaction and the temperature was gradually lowered to that required for the particular experiment. This must be done slowly otherwise Grignard formation stops. The formation of trifluoromethylmagnesium iodide is accompanied by a darkening of the solution and gradual deposition of a flocculent pale brown solid.

Note: It is strongly recommended that the conditions to be used for the preparation of trifluoromethylmagnesium iodide should be tested by use of heptafluoroiodopropane, from which Grignard formation is much more readily effected; if the conditions are such that a high yield (see Part I) of heptafluoropropylmagnesium iodide is not obtained, it is most unlikely that trifluoromethylmagnesium iodide will be prepared successfully when the same conditions are applied to trifluoroiodomethane.

(b) *Solvents.* (i) Trifluoroiodomethane (2·0 g.), magnesium (1·0—1·5 g.), and perfluoromethyl*cyclo*hexane (10—20 ml.) were heated in sealed tubes at temperatures from 50° to 250°. No significant reaction was detected below 150°, and at higher temperatures hexafluoroethane and magnesium iodide and fluoride were detected. Addition of water or of carbon dioxide, with or without an organic solvent, failed to produce fluoroform or trifluoroacetic acid. The formation of trifluoromethylmagnesium iodide could not be detected at temperatures up to 100° when benzene was used as solvent; at higher temperatures there was appreciable attack by trifluoromethyl radicals on benzene, but no formation of the Grignard compound.

(ii) The experiments summarised in Table 1 were carried out to determine the variation of yield with temperature and with solvent. Trifluoroiodomethane (5·0 g.), magnesium (2·5 g.), and solvent (150 ml.) were caused to react at the temperature indicated after initiation of reaction at 20°; the reaction time was 72 hr., and an atmosphere of carbon dioxide was used to remove the Grignard compound as soon as it was formed. The yields are based on the quantity of the fluoro-iodide taken and are the mean of at least two on this scale, the products being combined.

Trifluoroiodomethane could not be separated quantitatively from ethyl ether by trap-to-trap fractionation *in vacuo*, but distillation through a low-temperature column gave a satisfactory separation; conversion of the trifluoroiodomethane into fluoroform was sometimes used to estimate the amount of the fluoro-iodide recovered. The experiments reported are those in which Grignard formation was successfully initiated and the reaction continued when the mixture was cooled. In approx. 75% of the experiments either initiation of the reaction could not be effected, or, particularly at the lower temperatures, the reaction stopped when the tube was cooled; these experiments are not reported.

TABLE 1. *Yield* (%) *of Grignard compound, and, in parentheses, recovery* (%) *of starting material, at various temperatures.*

	−60°	−40°	−30°	−15°	0°	20°	40°	60°
Et_2O	38(25)	35(18)	39(19)	41(18)	36(13)	33(8)	26(4)	20(~2)
Bu_2O	33(20)	37(—)	27(31)	39(16)	42(11)	30(10)	25(—)	18(6)
$[CH_2]_5O$	29(28)	28(—)	39(15)	45(11)	44(12)	40(7)	21(—)	20(—)

These results are not as reproducible as those obtained with heptafluoroiodopropane (Part I), but reveal the decrease in yield with increase in reaction temperature, and indicate that tetrahydropyran is more suitable than dialkyl ethers except for temperatures below −40°.

(c) *Dilution.* The marked increase in decomposition in concentrated solutions is shown by the results in Table 2. Magnesium (2·0 g.), trifluoroiodomethane (5·0 g.), and ethyl ether were kept at −10° for 48 hr. after initiation of reaction at 20°.

TABLE 2.

Solvent (ml.)	5	10	20	50	100	150	500
CF_3I recovered (%)	26 *	20 *	—	19	17	15	31
CF_3·MgI formed (%)	0	12	29	37	41	43	21

* High yields of fluoroform obtained.

(d) *Temperature.* The effect of reaction temperature on yield is shown in Table 1. The rate of decomposition of trifluoromethylmagnesium iodide, prepared as in Table 1, but without a carbon dioxide atmosphere, is shown by the data of Table 3. Ethyl ether was used as solvent.

TABLE 3.

Temp.	−60°	−40°	−20°	0°	20°	40°
Time (hr.)	72	96	96	48	24	24
Decomp. (%)	6	21	33	35	75	80

(e) *Reaction with the second component.* It is often preferable to have the compound with which trifluoromethylmagnesium iodide is to react (*e.g.*, carbon dioxide) present in solution during formation of the Grignard reagent.

By-products. The volatile by-product arising during formation of trifluoromethylmagnesium iodide was fluoroform (Found: *M*, 70. Calc. for CHF_3: *M*, 70), identified later by means of its infra-red spectrum, and readily separated from unchanged reactants by distillation *in vacuo*. Hexafluoroethane was not a reaction product. The amount of fluoroform as by-product varied from 10—15% at −30° to 25—30% at 40°. Magnesium iodide and fluoride and a tetrafluoroethylene polymer were also produced. The last material was isolated by treatment of the insoluble products obtained by filtration of the Grignard-reagent solution with acid, base, and alcohol; when heated in a high vacuum, the pale brown solid gave a white sublimate [Found: C, 24·0; H, 0. Calc. for $(C_2F_4)_n$: C, 24·0; H, 0%]. The residual solid (*ca.* 80%) was polymer of greater molecular weight [Found: C, 23·9; H, 0%]. An infra-red spectrum of the solid which sublimed was very similar to that of polytetrafluoroethylene. When the polymer which did not sublime was pyrolysed in a platinum crucible at 700° in a high vacuum, a 53% yield of tetrafluoroethylene was obtained, and only a small carbonaceous residue remained; hexafluoropropene was also produced (5—10%), but other fluorine-containing products could not be identified spectroscopically.

Reactions of Trifluoromethylmagnesium Iodide.—(a) *Thermal decomposition.* A solution of trifluoromethylmagnesium iodide, prepared in 41% yield at −15° in ethyl ether as described above, was freed from fluoroform, filtered, then heated rapidly to vigorous reflux. Fluoroform (81%) and tetrafluoroethylene (6%) were produced, and a small amount of flocculent solid was deposited.

(b) *With water.* It was assumed that the reaction with aqueous reagents was quantitative.

(c) *With compounds which contain active hydrogen.* The yields of fluoroform when an excess of ethanol, methanol, *n*-butylamine, acetic acid, or anhydrous hydrogen chloride was added to solutions of the Grignard compound were essentially the same as when water was added.

(d) *With carbon dioxide.* In a typical experiment, spectroscopically pure magnesium shavings (3 g.; prepared under *n*-butyl ether) were freed from organic solvent by pumping *in vacuo* in a 500-ml. Pyrex tube and then heated with dry iodine as described earlier. After cooling, *n*-butyl ether (150 ml.) was condensed into the tube *in vacuo*, followed by methyl iodide (0·5 g.) and trifluoroiodomethane (10·0 g.). Dry carbon dioxide was condensed into the tube, which was then sealed *in vacuo* and allowed to warm to room temperature; the pressure of carbon dioxide was *ca.* 5 atm. The tube was shaken vigorously at 20° for 30 min. before reaction could be detected by formation of a light brown flocculent precipitate and darkening of the solution. The reaction at 20° was allowed to proceed for 10 min. to ensure that trifluoroiodomethane was reacting as well as methyl iodide, and the tube was then cooled (20 min.) to −10° at which temperature it was kept for 12 hr. The tube was then cooled by liquid oxygen, opened, recharged with carbon dioxide, and kept at 20° for 30 min., then at −10° for 30 hr. The tube was warmed stepwise to 40° during 12 hr., then frozen in liquid oxygen and opened. The products with b. p. <0° were fractionated *in vacuo* and shown to be carbon dioxide, trifluoroiodomethane (12%), and fluoroform (12%); carbon dioxide was

absorbed by aqueous alkali to enable the fluoroform to be separated. The contents of the reaction vessel were filtered in absence of air to remove the excess of magnesium, magnesium fluoride, polymer, etc., and to the filtrate were added water (20 ml.), then 5N-hydrochloric acid (100 ml.). Fluoroform (6%) was evolved, showing that the trifluoromethylmagnesium iodide had not all reacted. The ethereal layer was extracted with aqueous sodium hydroxide, and the aqueous layer was filtered and extracted with ethyl ether, and the ethereal extract concentrated in presence of 5N-sodium hydroxide. The combined aqueous alkaline extracts were neutralised (bromothymol-blue) and evaporated to dryness *in vacuo*. Extraction with hot ethanol gave sodium trifluoroacetate, converted into the acid (39% based on trifluoroiodomethane taken; *ca.* 80% based on CF_3·MgI), b. p. 70—72°, and thence into the silver salt (37%), identified by comparison with a genuine specimen prepared earlier. The resinous material obtained at the filtration stage was treated with acid as described above, to give a polytetrafluoroethylene-type polymer (12%). Distillation of the butyl ether after extraction with aqueous sodium hydroxide gave a residue which contained covalent fluorine, but attempts to isolate definite products were unsuccessful.

In the following experiments trifluoromethylmagnesium iodide was prepared in ethyl- or butyl-ethereal solution at a temperature between 0° and −30°. The yield of the Grignard compound was derived from the data recorded earlier, or, when the completeness of the Grignard reaction was in doubt, by measuring the fluoroform evolved on hydrolysis of an aliquot. The filtered solution of the Grignard reagent was used for the reaction described. Fluoroform was removed in all instances before reaction with the second component. The solvent was chosen to make separation of reaction products easy. Unchanged trifluoroiodomethane, which could not be separated completely from ethyl ether, was present during some reactions, but did not interfere.

(e) *With methyl iodide.* Reaction of trifluoromethylmagnesium iodide (3·0 g.) with an excess of methyl iodide was investigated in experiments at −30°, −10°, 0°, 20°, and 40°, but 1 : 1 : 1-trifluoroethane was not detected as a product; fluoroform was produced by thermal decomposition of the Grignard compound.

(f) *With acetonitrile.* To trifluoromethylmagnesium iodide (4·5 g.) was added a solution of acetonitrile (2·5 g.) in butyl ether (10 ml.) in three portions. Between each addition the reaction tube was sealed, shaken, and warmed from −25° to +10° (1 hr.); the next portion was then added. Finally the reaction tube was vigorously shaken and heated to 50° (3 hr.). When it was cool, an excess of 10N-sulphuric acid was added cautiously. The volatile products were distilled *in vacuo*, to give 1 : 1 : 1-trifluoroacetone (15%) (Found: *M*, 112. Calc. for $C_3H_3OF_3$: *M*, 112), b. p. 21°. The ethereal extracts were dried (P_2O_5) and distilled, to give a further amount of trifluoroacetone (17%). The aqueous solution yielded the 2 : 4-dinitrophenylhydrazone of trifluoroacetone (6%).

(g) *Trifluoroacetonitrile.* The nitrile was prepared by dehydration of trifluoroacetamide with phosphoric anhydride. To trifluoroacetonitrile (4·3 g.) frozen in three Carius tubes was added a solution of trifluoromethylmagnesium iodide (9·7 g.) in butyl ether (100 ml.). The tubes were sealed, and kept at −20° for 3 days with intermittent shaking. The temperature was then slowly raised to 30° (2 days), before addition of sulphuric acid as in (f) above. Hexafluoroacetone was not present in the volatile products, but was isolated from the combined ethereal and aqueous layers as follows: The ethereal layer was separated, combined with the ethereal extracts (5) of the residual aqueous layer, and distilled from a small amount of phosphoric anhydride, to give hexafluoroacetone hydrate containing water, b. p. 50—60°/35 mm., and a small amount of hexafluoroacetone. These substances, together with the small amount of butyl ether which had distilled over, were combined and treated with an excess of phosphoric anhydride in a sealed tube at 80° (3 hr.). Distillation *in vacuo* gave hexafluoroacetone (33% based on CF_3·MgI), b. p. −28° (Found: *M*, 166. Calc. for C_3OF_6: *M*, 166), identified by means of its semicarbazone, m. p. 154° (decomp.). Fukuhara and Bigelow (*J. Amer. Chem. Soc.*, 1941, **63**, 788) report m. p. 153° (decomp.).

(h) *Ethylene oxide.* Ethylene oxide (2·5 g.) was condensed into a tube containing trifluoromethylmagnesium iodide (6·8 g.) in ethyl ether (130 ml.), and after being sealed the tube was kept at 0° for 12 hr., then warmed to 40° during 30 hr. A polymeric material could be seen on the walls of the tube. Sulphuric acid (5N) was added to the tube, and the ethereal layer was separated. Ethereal extracts (twice) of the aqueous layer were combined with the original ethereal layer and, after being dried (P_2O_5), were distilled, to give 3 : 3 : 3-trifluoropropan-1-ol (57%), b. p. 100—101° (Found: C, 31·2; H, 4·6. Calc. for $C_3H_5OF_3$: C, 31·6; H, 4·4%). For further identification the alcohol was oxidised by chromic anhydride–sulphuric acid (cf.

Part II), to give βββ-trifluoropropionic acid, b. p. 145° (Found: equiv., 127. Calc. for $C_3H_3O_2F_3$: equiv., 128).

Reaction of Trifluoromethylmagnesium Iodide with Acyl Chlorides.—The following general procedure was adopted to obtain maximum yields of ketones. The acid chloride (prepared by interaction of the corresponding acid and phosphorus pentachloride in the usual way) was condensed from a vacuum-system into the reaction vessel which was cooled in liquid oxygen. A solution of trifluoromethylmagnesium iodide (4—5 g.) was then added, and whilst still frozen the tube was sealed off. A two-molar excess of acyl halide was used. The mixture was heated stepwise from −30° to 40° during 7 days, and the volatile products were transferred to a vacuum-system. The ketones of higher b. p. were isolated from the ethereal solution by distillation. Yields are based on trifluoromethylmagnesium iodide. No attempt was made to investigate the other reaction products.

(a) *Acetyl chloride.* **1 : 1 : 1-Trifluoroacetone** was isolated by distillation *in vacuo* (59%), b. p. 21° (Found: *M*, 111. Calc. for $C_3H_3OF_3$: *M*, 112), identical with the compound obtained above.

(b) *Propionyl chloride.* Butyl ether has to be used to enable the ketone to be isolated easily. The product, **1 : 1 : 1-*trifluorobutan*-2-*one*** (47%), b. p. 46° (Found: C, 38·3; H, 4·7%; *M*, 126. $C_4H_5OF_3$ requires C, 38·1; H, 4·0%; *M*, 126), is an isomer of the 4 : 4 : 4-trifluorobutan-2-one, b. p. 95—96°, obtained by the hydration of 1 : 1 : 1-trifluorobut-2-yne (Haszeldine and Leedham, *J.*, 1954, 1261). Its 2 : 4-*dinitrophenylhydrazone* (Found: C, 39·0; H, 3·2; N, 18·3. $C_{10}H_9O_4N_4F_3$ requires C, 39·2; H, 3·0; N, 18·3%), m. p. 93°, has ultra-violet absorption maxima in EtOH at 336, 254, and 220 mμ (ε 20,000, 12,000, 13,500), and minima at 288 and 238 mμ (ε 4500, 11,400). The isomeric ketones are readily distinguished by means of their b. p.s, the m. p.s and ultra-violet spectra of their 2 : 4-dinitrophenylhydrazones, and their infra-red spectra; CF_3·COEt shows C:O absorption at 5·62 μ (cf. CF_3·COMe, 5·61 μ) and CF_3·CH_2·COMe at 5·72 μ. The ultra-violet spectrum of 1 : 1 : 1-trifluorobutan-2-one vapour ($\lambda_{max.}$ 286·5, ε 8·9; $\lambda_{min.}$ 236·5, ε 2·2) is very similar to that of 4 : 4 : 4-trifluorobutan-2-one ($\lambda_{max.}$ 286, ε 7·5; $\lambda_{min.}$ 242, ε 2·9). Barkley and Levine (Abs. Amer. Chem. Soc. Meeting, 1952, 5M) prepared 1 : 1 : 1-trifluorobutan-2-one by an alternative route.

(c) *Butyryl chloride.* This gave **1 : 1 : 1-*trifluoropentan*-2-*one*** (51%) b. p. 68° (Found: C, 42·6; H, 4·8%; *M*, 140. $C_5H_7OF_3$ requires C, 42·8; H, 5·0%; *M*, 140), characterised as its 2 : 4-*dinitrophenylhydrazone*, m. p. 74° (Found: N, 17·7. $C_{11}H_{11}O_4N_4F_3$ requires N, 17·5%). Barkley and Levine (*loc. cit.*) have prepared this ketone by an alternative route (b. p. 65°/735 mm.; personal communication).

(d) *Trifluoropropionyl chloride.* This reaction, carried out with the acyl halide (2·3 g.) and trifluoromethylmagnesium iodide (2·5 g.), with conditions as described above, gave **1 : 1 : 1 : 4 : 4 : 4-hexafluorobutanone** (37%), b. p. 54—55° (Found: *M*, 179. Calc. for $C_4H_2OF_6$: *M*, 180), identified by means of its infra-red spectrum.

(e) *Monofluoroacetyl chloride.* This reaction was carried out in a fume-chamber. A four-molar excess of the acyl chloride was used, since an initial experiment showed that it or the resultant ketone was readily decomposed to magnesium fluoride and chloride by the Grignard compound. **1 : 1 : 1 : 3-Tetrafluoroacetone**, isolated in 15% yield, had b. p. 45—46° (Found: C, 27·3; H, 1·6%; *M*, 128. Calc. for $C_3H_2OF_4$: C, 27·7; H, 1·5%; *M*, 130). McBee, Pierce, Kilbourne, and Wilson (*J. Amer. Chem. Soc.*, 1953, **75**, 3152) prepared this ketone from the corresponding acetylacetone.

(f) *Difluoroacetyl chloride.* The acyl halide did not lose fluoride when treated with the Grignard compound, and the usual reactant ratio was used to give **pentafluoroacetone** (59%), b. p. 4° (isoteniscope) (Found: C, 24·2; H, 0·7%; *M*, 148. Calc. for C_3HOF_5: C, 24·3; H, 0·7%; *M*, 148). McBee *et al.* (*loc. cit.*) report b. p. 2—3°.

(g) *Trifluoroacetyl chloride.* The conditions were as before, except that the temperature was raised from −15° to 50° during 8 days. Butyl ether is the most suitable solvent. The **hexafluoroacetone** (49%) was identified as described above, and as its 2 : 4-dinitrophenylhydrazone.

(h) Heptafluorobutyryl chloride was similarly treated, to give **perfluoropentan-2-one** (43%), b. p. 30° (Found: *M*, 266. Calc. for C_5OF_{10}: *M*, 266), identical with the compound isolated in Part II (*loc. cit.*).

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Colouring Matters of the Aphididæ. Part IX. Some Reactions of Extended Quinones.*

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The reactions of some " extended " quinones with amines and with alkali in presence of air have been examined. Perylene-3 : 10-quinone reacts with *cyclo*hexylamine, piperidine, and sodium hydroxide solution in presence of air to give respectively 1-*cyclo*hexylamino-, 1-piperidino-, and 1-hydroxyperylene-3 : 10-quinone. Details in the infra-red spectrum of the last-named compound are discussed and 2 : 11-dihydroxyperylene-3 : 10-quinone is also shown to yield a monopiperidino-derivative. These findings support the view expressed in earlier papers from this laboratory that the erythroaphins are derivatives of perylene-3 : 10-quinone.

On the basis of all available evidence it was postulated in Part VII of this series (Brown, Johnson, MacDonald, Quayle, and Todd, *J.*, 1952, 4298) that the erythroaphins, a group of deep red colouring matters derived from a variety of dark-coloured aphids, are extended quinones (*i.e.*, polycyclic quinones in which the carbonyl groups occur in different rings) in which the quinonoid carbonyls are in peripheral rings of the polycyclic system. The simplest of such structures formulates them as derivatives of perylene-3 : 10-quinone. A significant factor in arriving at this conclusion was the ease with which erythroaphin-*fb* appeared to undergo the Thiele acetylation reaction and to react with ammonia or amines in presence of air giving diamino- or substituted diamino-derivatives. Such reactions are typical of simple *p*-quinones (Leicester, *Ber.*, 1890, **23**, 2793) and *meso*benzanthrones (Bradley and Sutcliffe, *J.*, 1952, 1247) but, apart from the fact that 3 : 5 : 3′ : 5′-tetramethyldiphenoquinone (I; R = Me) undergoes the Thiele acetylation reaction (Erdtman, *Proc. Roy. Soc.*, *A*, 1933—34, **143**, 177), no record of similar behaviour among extended quinones exists. Indeed, such quinones as diphenoquinone (I; R = H) and perylene-3 : 10-quinone (II; R = H) have been little studied, possibly owing to the difficulty involved in preparing them in quantity. It was therefore necessary to examine their reactions in order to establish whether they undergo reactions with nucleophilic reagents in a manner analogous to the erythroaphins, as an aspect of structural studies on the aphid colouring matters.

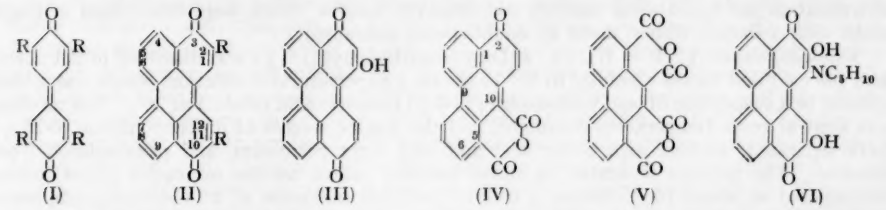
Diphenoquinone (I; R = H) was prepared by a new method, *viz.*, oxidation of 4 : 4′-dihydroxydiphenyl with lead tetra-acetate in glacial acetic acid at room temperature. The yield was about 75% and the method proved much superior to that of Willstätter and Kalb (*Ber.*, 1905, **38**, 1235) which employed lead dioxide in benzene. Fieser (*J. Amer. Chem. Soc.*, 1930, **52**, 5204) has recorded for diphenoquinone the very high oxidation–reduction potential of 954 mv, indicative of great reactivity as an oxidising agent. It was therefore not surprising to find that diphenoquinone would not undergo addition reactions with amines; reaction with *cyclo*hexylamine, piperidine, or morpholine in air at room temperature yielded only its reduction product 4 : 4′-dihydroxydiphenyl. In the same way it yielded only 4 : 4′-diacetoxydiphenyl under the conditions normally employed for Thiele acetylation. 3 : 5 : 3′ : 5′-Tetramethyldiphenoquinone (I; R = Me) has a lower oxidation–reduction potential (calculated to be *ca.* 754 mv) but, although it undergoes Thiele acetylation (Erdtman, *loc. cit.*), reaction with *cyclo*hexylamine, piperidine, or morpholine in air yielded only its reduction product 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenyl.

Perylene-3 : 10-quinone (II; R = H), however, with a lower oxidation–reduction potential of 534 mv (Gupta, *J.*, 1952, 3479) reacts readily with *cyclo*hexylamine or piperidine at 100° in presence of air, to give mono*cyclo*hexylamino- or monopiperidino-derivatives, and with alkali in presence of air to yield a monohydroxyperylene-3 : 10-quinone. The

* Part VIII, *J.*, 1954, 107.

same monohydroxy-quinone is formed on hydrolysis of the mono*cyclo*hexylamino-quinone, indicating that the hydroxy- and amino-compounds have the same orientation.

2 : 11-Dihydroxyperylene-3 : 10-quinone (II; R = OH) condenses readily with 2 mols. of *o*-phenylenediamine, a fact taken to prove the location of the hydroxyl groups in this compound (Zinke, Stimler, and Reuss, *Monatsh.*, 1934, **64**, 415). With *o*-phenylenediamine under the same conditions the monohydroxyperylene-3 : 10-quinone obtained above does not react and can be recovered unchanged. This observation indicates that the compound should be formulated as 1-hydroxyperylene-3 : 10-quinone (III) and that the *cyclo*hexylamino- and piperidino-compounds are also 1-substituted compounds. This conclusion is supported by the fact that in the reactions described perylene-3 : 10-quinone



yields only monosubstituted derivatives. If the substituent group entered the 2-position it would be expected that under the conditions employed (*i.e.*, in presence of excess of reagent and air) the quinone would yield a 2 : 11-disubstituted product (II; R = OH, *cyclo*hexylamino, or piperidino). On the other hand, examination of models shows that with the first substituent in the 1-position it would be very difficult on steric grounds to introduce a second substituent into the other angular (*i.e.*, 12-) position. Moreover, substitution in the 1-position occurs readily in 2 : 11-dihydroxyperylene-3 : 10-quinone (II; R = OH) which, with piperidine, yields 2 : 11-dihydroxy-1-piperidinoperylene-3 : 10-quinone (VI).

Perylene-3 : 10-quinone undergoes Thiele acetylation but the course of reaction is unusual. Treatment with acetic anhydride and perchloric acid at 35° for several days, followed by hydrolysis and aerial oxidation, gave a compound which from its analysis and infra-red spectrum appeared to be identical with that formulated by Zinke, Hirsch, and Brodek (*Monatsh.*, 1929, **51**, 205) as perylene-3 : 4 : 9 : 10-diquinone. Further discussion of the true nature of this compound is reserved for a later communication.

Oxidation of perylene-3 : 10-quinone with potassium permanganate in aqueous pyridine yielded 2-oxobenzanthrene-5 : 10-dicarboxylic anhydride (IV) and phenanthrene-1 : 8 : 9 : 10-tetracarboxylic dianhydride (V); it seems likely that 1-hydroxyperylene-3 : 10-quinone is an intermediate in this oxidation.

In agreement with observations recorded for other extended quinones (Josien and Fuson, *J. Amer. Chem. Soc.*, 1951, **73**, 478; Hadzi and Sheppard, *ibid.*, p. 5460; Johnson, Quayle, Robinson, Sheppard, and Todd, *J.*, 1951, 2633) the carbonyl frequency in the infra-red spectrum of perylene-3 : 10-quinone (1650 cm.$^{-1}$) was found to be lower than that of a simple *p*-quinone (1660—1680 cm.$^{-1}$). In 2 : 11-dihydroxyperylene-3 : 10-quinone the carbonyl frequency is shifted even further (1621 cm.$^{-1}$) owing to the presence of the *o*-hydroxyl groups. However, unlike quinones with *peri*-hydroxyl groups (Flett, *J.*, 1948, 1441; Johnson *et al.*, *loc. cit.*) the shift is not accompanied by disappearance of the hydroxyl frequency (*ca.* 3300 cm.$^{-1}$), for 2 : 11-dihydroxyperylene-3 : 10-quinone shows a strong hydroxyl band at 3280 cm.$^{-1}$. The compound here formulated as 1-hydroxyperylene-3 : 10-quinone shows a double carbonyl band with maxima at 1647 and 1621 cm.$^{-1}$ and a strong hydroxyl band at 3322 cm.$^{-1}$. A similar splitting of the carbonyl band is observed in 2-hydroxynaphthalene-1 : 4-quinone which shows maxima at 1680 and 1645 cm.$^{-1}$, as well as a hydroxyl band at 3080 cm.$^{-1}$. That the lowering of the carbonyl frequency is due to electron distribution and not solely to chelation is indicated by the facts that the hydroxyl frequency, though modified, does not disappear completely as it does in quinones having *peri*-hydroxyl groups, and that compounds which have no hydrogen available for

chelation still show the effect, *e.g.*, the carbonyl frequency for *p*-benzoquinone is 1660 cm.$^{-1}$ whereas for 2 : 5-bisdimethylamino-*p*-benzoquinone it is 1630 cm.$^{-1}$.

The infra-red data quoted cannot be used to differentiate between 1- and 2-substituted perylene-3 : 10-quinones since resonance can operate equally well for substituents in both these positions. Analogous effects have been observed in 2-aminoanthraquinone (Flett, *loc. cit.*) and in *o*-substituted acetophenones (Hegert and Kurth, *J. Amer. Chem. Soc.*, 1953, **75**, 1622).

Experimental

Since the majority of the compounds described do not have m. p.s, characterisation and identification are based upon analysis and infra-red spectra, which were determined in Nujol mulls with a Perkin–Elmer Model 21 double-beam instrument.

Diphenoquinone (I; R = H).—4 : 4′-Dihydroxydiphenyl (1·0 g.) was dissolved in hot acetic acid (60 c.c.) and cooled carefully to 30° to obtain a supersaturated solution, which was added quickly to a suspension of lead tetra-acetate (3·0 g.) in acetic acid (40 c.c.) at 30°. The mixture was kept at room temperature overnight, and the scarlet needles of diphenoquinone (0·75 g.) were separated, washed with acetic acid and with light petroleum, and recrystallised from benzene. The quinone separated as either feathery yellow needles or scarlet plates, which decomposed at about 160° yielding a white crystalline sublimate of 4 : 4′-dihydroxydiphenyl and a refractory brown residue (Found: C, 78·4; H, 4·6. Calc. for $C_{12}H_8O_2$: C, 78·3; H, 4·4%). Light absorption in $CHCl_3$: max. at 253, 263, and 398 mμ; log ε 3·40, 3·37, and 4·84 respectively; min. at 249, 260, and 270 mμ; log ε 3·29, 3·17, and 2·51 respectively. The infra-red spectrum showed max. at 722, 736, 786, 857, 968, 992, 1107, 1171, 1258, 1282, 1550, 1597, and 1639 cm.$^{-1}$.

3 : 5 : 3′ : 5′-*Tetramethyldiphenoquinone* (I; R = Me).—Prepared according to Bamberger (*Ber.*, 1903, **36**, 2036), the quinone separated from acetic acid as small red needles, m. p. 208° (decomp.). The infra-red spectrum showed max. at 722, 775, 830, 913, 939, 1047, 1218, 1250, 1277, 1563, 1597, and 1645 cm.$^{-1}$.

Perylene-3 : 10-*quinone* (II; R = H).—Prepared according to Zinke and Unterkreuter (*Monatsh.*, 1919, **40**, 405), the quinone separated from nitrobenzene as yellow needles (Found, in material dried at 180°/0·2 mm. for 20 hr.: C, 84·8; H, 3·5. Calc. for $C_{20}H_{10}O_2$: C, 85·1; H, 3·6%). Light absorption in concentrated H_2SO_4: max. at 285, 347, 362, 489, and 584 mμ; log ε 4·12, 3·70, 3·71, 4·57, and 3·84 respectively; min. at 271, 315, 354, 375, and 569 mμ; log ε 4·01, 3·48, 3·64, 3·06, and 3·73 respectively; infl. at 543 mμ; log ε 4·01. The infra-red spectrum showed max. at 763, 792, 844, 896, 1036, 1054, 1149, 1190, 1259, 1294, 1339, 1353, 1560, 1590, 1603, and 1650 cm.$^{-1}$.

3 : 10-*Diacetoxyperylene*.—Perylene-3 : 10-quinone (300 mg.), acetic anhydride (25 c.c.), and excess of zinc dust were boiled under reflux for 2 hr. and filtered hot. The residue was extracted with hot acetic anhydride (25 c.c.). The combined filtrate and extracts yielded 3 : 10-*diacetoxyperylene* (288 mg.) as yellow plates, m. p. 265—270° (decomp.) after recrystallisation from acetic anhydride (Found, in material dried at 140°/0·1 mm. for 16 hr.: C, 78·1; H, 4·3. $C_{24}H_{16}O_4$ requires C, 78·2; H, 4·4%). Solutions of the compound in organic solvents are yellow with a strong blue fluorescence. Light absorption in $CHCl_3$: max. at 323, 325, 328, 396, 419, and 446 mμ; log ε 2·89, 2·90, 2·89, 4·11, 4·45, and 4·54 respectively; min. at 319, 324, 327, 333, 403, and 430 mμ; log ε 2·87, 2·88, 2·89, 2·87, 4·06, and 4·20 respectively; infl. at 374—378 mμ; log ε 3·68. The infra-red spectrum showed max. at 692, 760, 769, 803, 811, 870, 920, 938, 1007, 1021, 1036, 1076, 1129, 1143, 1157, 1182, 1209, 1220, 1282, 1309, 1391, 1506, 1603, and 1764 cm.$^{-1}$.

2-*Oxobenzanthrene*-5 : 10-*dicarboxylic Anhydride* (IV) (Zinke and Wenger, *Monatsh.*, 1930, **56**, 147).—Sublimation at 260°/5 × 10^{-3} mm. yielded orange-brown needles (Found: C, 75·6; H, 2·7. Calc. for $C_{19}H_8O_4$: C, 76·0; H, 2·7%). Light absorption in concentrated H_2SO_4: max. at 230, 311, and 470 mμ; log ε 4·56, 3·98, and 4·37 respectively; min. at 215, 290, and 363 mμ; log ε 4·49, 3·86, and 3·18 respectively; infl. at 278—283 mμ; log ε 3·88. Light absorption in N-NaOH: max. at 266, 297, 309, 424, and 474 mμ; log ε 4·36, 4·00, 3·99, 4·14, and 4·07 respectively; min. at 254, 292, 304, 326, and 463 mμ; log ε 4·27, 3·98, 3·88, 3·52, and 3·97 respectively. The infra-red spectrum showed max. at 729, 742, 768, 811, 841, 873, 917, 932, 970, 1031, 1053, 1093, 1115, 1144, 1181, 1200, 1241, 1277, 1294, 1330, 1577, 1608, 1645, 1736, and 1770 cm.$^{-1}$.

Aerial Oxidation of Perylene-3 : 10-*quinone in Alkaline Solution*.—Sodium hydroxide solu-

tion (300 c.c.; 10%) was added to a hot suspension of finely powdered perylene-3 : 10-quinone (1·0 g.) in dioxan (250 c.c.), and the mixture was heated under reflux for 6 hr. The solution quickly became deep purple and then deep green. Air was passed through the mixture for 5 hr. and the dioxan allowed to evaporate slowly. The solution was cooled overnight, and the insoluble black sodium salt was collected and washed with 10% sodium hydroxide solution until the washings no longer showed an oily green fluorescence. Extraction of the sodium salt with boiling water yielded a deep green non-fluorescent solution which gave a dark brown precipitate when excess of dilute sulphuric acid was added. The dry precipitate was recrystallised several times from nitrobenzene, to yield a black crystalline powder (0·60 g.) (Found, in material dried at 150°/0·05 mm. for 21 hr.: C, 79·0; H, 3·5%). Successive crystallisations from nitrobenzene effected no further purification. The compound was therefore reductively acetylated.

1 : 3 : 10-*Triacetoxyperylene*.—The above crude hydroxy-quinone (200 mg.) was boiled under reflux with acetic anhydride (50 c.c.), sodium acetate (200 mg.), and excess of zinc dust for 2 hr. Filtration yielded a reddish-brown solution with a bluish-green fluorescence, which was stirred with ice-cold sodium acetate solution for 1 hr., and the dark brown solid was collected, washed, and dried *in vacuo* over phosphoric oxide at room temperature. The crude acetoxy-compound was dissolved in benzene (50 c.c.) and put on a column of silica (5·5 × 15 cm.). The impurities formed an upper dark brown band, and the product was eluted with benzene (2 l.) as a yellow, blue-fluorescent band. Evaporation of the benzene, a repetition of chromatography on silica, and several recrystallisations from acetic anhydride or benzene yielded 1 : 3 : 10-*triacetoxyperylene* (130 mg.) as bright yellow, small, hair-like needles, m. p. 238—239° (decomp.) (Found: C, 73·3, 73·1, 73·5; H, 4·2, 4·3, 4·5. $C_{26}H_{18}O_6$ requires C, 73·3; H, 4·2%). The compound is readily soluble in chloroform, yielding a yellow solution with a blue fluorescence. Light absorption in $CHCl_3$: max. at 250, 256, 296, 308, 397, 419, and 446 mμ; log ε 4·66, 4·68, 4·03, 3·98, 4·22, 4·46, and 4·52 respectively; min. at 251, 292, 304, 328, 402, and 430 mμ; log ε 4·65, 4·02, 3·96, 3·71, 4·19, and 4·26 respectively. The infra-red spectrum showed max. at 743, 761, 769, 781, 804, 825, 838, 856, 872, 895, 915, 990, 1024, 1081, 1100, 1148, 1160, 1205, 1600, and 1770 cm.$^{-1}$.

1-*Hydroxyperylene*-3 : 10-*quinone* (III).—1 : 3 : 10-Triacetoxyperylene in chloroform was treated with methanol containing a few drops of 10% aqueous sodium hydroxide. The solution immediately became deep blue and deposited a blue sodium salt. This salt was dissolved in water and treated with excess of dilute sulphuric acid, and the mixture shaken with air. The orange-red precipitate was sublimed at 260°/5 × 10^{-3} mm., to yield 1-*hydroxyperylene*-3 : 10-*quinone* as flat red needles, which did not melt below 350° (Found: C, 80·0; H, 3·3. $C_{20}H_{10}O_3$ requires C, 80·6; H, 3·4%). Light absorption in concentrated H_2SO_4 (magenta solution): max. at 219, 237, 304, and 508 mμ; log ε 4·54, 4·51, 4·08, and 4·37 respectively; min. at 229, 375, and 370 mμ; log ε 4·49, 3·95, and 3·30 respectively. The infra-red spectrum showed max. at 703, 763, 811, 843, 849, 873, 896, 1008, 1099, 1176, 1244, 1299, 1414, 1582, 1621, 1647, and 3322 cm.$^{-1}$.

1-cyclo*Hexylaminoperylene*-3 : 10-*quinone*.—Perylene-3 : 10-quinone (200 mg.) was heated at 80° for 24 hr. with pyridine (20 c.c.) and *cyclo*hexylamine (10 c.c.). The resulting deep purple solution was diluted with water, and the product extracted with chloroform. The extract was washed free from pyridine and *cyclo*hexylamine with dilute sulphuric acid and water, dried, evaporated to small bulk (4 c.c.), and diluted with hot methanol (16 c.c.). 1-cyclo*Hexylaminoperylene*-3 : 10-*quinone* (217 mg.) separated as clusters of flat purple needles having a red-brown metallic sheen. The compound was recrystallised from methanol–chloroform or from anhydrous methanol (Found, in material dried at 100°/0·5 mm. for 24 hr.: C, 82·0, 82·0; H, 5·0, 5·4; N, 3·8, 3·8. $C_{26}H_{21}O_2N$ requires C, 82·4; H, 5·4; N, 3·7%). The compound, which on being heated decomposes without melting, is hygroscopic and in air absorbs water to constant weight (Found: C, 80·8; H, 5·4; N, 3·75. $C_{26}H_{21}O_2N,\frac{1}{2}H_2O$ requires C, 80·4; H, 5·7; N, 3·6%). It is soluble in acetic acid or chloroform, giving purplish-blue solutions. Its solution in concentrated sulphuric acid is blood-red with a red fluorescence; on dilution with water the colour changes to deep green and a green sulphate separates; further dilution yields the original purple solid. Light absorption in $CHCl_3$: max. at 285, 328, 402, 454, 490, 568, 578, and 586 mμ; log ε 4·55, 3·92, 4·21, 3·78, 3·90, 4·29, 4·30, and 4·30 respectively; min. at 323, 339, 444, 467, 497, 570, and 580 mμ; log ε 3·87, 3·56, 3·76, 3·73, 3·89, 4·29, and 4·29 respectively; infl. at 498—500 and 572—576 mμ; log ε 3·89 and 4·29. Light absorption in concentrated H_2SO_4; max. at 341—343, 488, and 558 mμ; log ε 3·77, 4·54, and 3·99 respectively; min. at 310, 376, and 553, mμ; log ε 3·60, 3·61, and 3·97 respectively; infl. at 354—357 mμ; log ε 3·71.

The infra-red spectrum showed max. at 769, 807, 1028, 1122, 1232, 1244, 1292, 1335, 1515, 1563, 1587, 1603, 1645, and 3300 cm.$^{-1}$.

Hydrolysis of 1-cyclo*Hexylaminoperylene*-3 : 10-*quinone*.—Sodium hydroxide solution (20 c.c.; 5%) was added to a boiling solution of *cyclo*hexylaminoperylene-3 : 10-quinone (200 mg.) in dioxan (20 c.c.), and the mixture was boiled under reflux for 5½ hr. The cooled mixture was filtered, the bluish-purple solid washed with water, and the alkaline filtrate washed with chloroform until free from purple starting material. From the residual purple solid and the chloroform extracts, unchanged crystalline *cyclo*hexylaminoperylene-3 : 10-quinone (60 mg.) was isolated. The deep green, non-fluorescent, alkaline filtrate was acidified, and the brown precipitate separated, dried, and recrystallised several times from boiling nitrobenzene. 1-Hydroxyperylene-3 : 10-quinone (24 mg.) was obtained as reddish-brown rectangular plates (Found, in material dried at 170°/4 × 10^{-4} mm. for 6 hr. : C, 79·8; H, 3·7. Calc. for $C_{20}H_{10}O_3$: C, 80·6; H, 3·4%). The compound was identical with 1-hydroxyperylene-3 : 10-quinone in its ultra-violet and infra-red spectra.

1-*Piperidinoperylene*-3 : 10-*quinone*.—Perylene-3 : 10-quinone (88 mg.) was heated at 80° with redistilled piperidine (10 c.c.) for 45 min. The quinone dissolved and a deep purple solution resulted, which deposited purple crystals (45 mg.) on being cooled to 0°. Recrystallisation from pyridine–methanol (1 : 1) yielded 1-*piperidinoperylene*-3 : 10-*quinone* as small purple plates which decomposed without melting; the crystals had a brown reflex. In air the compound absorbed water to constant weight (Found : C, 80·4, 80·9, 80·5; H, 5·0, 5·3, 5·0; N, 3·6, 3·7. $C_{25}H_{19}O_2N,\frac{1}{2}H_2O$ requires C, 80·3; H, 5·4; N, 3·8%). Light absorption in concentrated H_2SO_4 (blood-red solution) : max. at 340 and 486 mμ; log ε 3·73 and 4·50; min. at 308 and 376 mμ; log ε 3·64 and 3·45; infl. at 324—336 mμ log ε 3·71. Light absorption in $CHCl_3$: max. at 280, 401, 476, and 542 mμ; log ε 4·28, 4·22, 3·98, and 4·09; min. at 254, 343, 454, and 492; log ε 4·20, 3·73, 3·92, and 3·97; infl. at 434—444 mμ; log ε 3·94. The infra-red spectrum showed max. at 768, 781, 809, 835, 851, 864, 895, 986, 1033, 1049, 1088, 1104, 1133, 1188, 1239, 1247, 1294, 1332, 1553, 1585, and 1637 cm.$^{-1}$.

Permanganate Oxidation of Perylene-3 : 10-*quinone*.—A mixture of finely powdered perylene-3 : 10-quinone (400 mg.), finely powdered potassium permanganate (400 mg.), redistilled pyridine (30 c.c.), and a few drops of water was heated at 90° for 30 min., and filtered hot from manganese dioxide. The yellow filtrate, which had a strong green fluorescence, was kept at 0° for 45 min. and the brownish-yellow needles (30 mg.) of unchanged perylenequinone were separated. The manganese dioxide was washed with hot dilute sodium hydroxide solution, and the combined filtrate and washings were cooled and acidified. The resulting brown solid was crystallised from nitrobenzene, to yield orange needles (40 mg.) (Found, in material dried at 120°/0·5 mm. for 20 hr. : C, 75·8; H, 2·7. Calc. for $C_{19}H_8O_4$: C, 76·0; H, 2·7%). This compound was identical with 2-oxobenzanthrene-5 : 10-dicarboxylic anhydride (IV) in its infra-red and ultra-violet spectra.

Addition of methanol to the hot nitrobenzene mother-liquor from the above crystallisation yielded bronze needles (60 mg.) of phenanthrene-1 : 8 : 9 : 10-tetracarboxylic dianhydride (V) (Found, in material dried at 170°/0·2 mm. for 15 hr. : C, 68·0; H, 2·2. Calc. for $C_{18}H_6O_6$: C, 67·9; H, 1·9%). Light absorption in concentrated H_2SO_4 : max. at 303, 314, and 406 mμ; log ε 4·05, 4·06, and 4·16 respectively; min. at 276, 305, and 315 mμ; log ε 3·86, 4·02, and 3·48 respectively. Light absorption in aq. NaOH : max. at 265, 305, and 315 mμ; min. at 238, 291, and 312 mμ. The infra-red spectrum showed max. at 730, 741, 760, 775, 807, 833, 864, 885, 904, 940, 979, 1017, 1045, 1091, 1103, 1133, 1149, 1152, 1205, 1245, 1264, 1282, 1339, 1401, 1636, 1575, 1592, 1608, 1667, 1745, and 1779 cm.$^{-1}$.

2 : 11-*Dihydroxyperylene*-3 : 10-*quinone* (II; R = OH). Prepared according to Zinke, Stimler, and Reuss (*Monatsh.*, 1933, **62**, 415) and recrystallised several times from nitrobenzene, the dihydroxy-quinone formed minute black crystals (Found, in material dried at 150°/1·0 mm. for 18 hr. : C, 76·4; H, 3·5. Calc. for $C_{20}H_{10}O_4$: C, 76·4; H, 3·2%). Light absorption in concentrated H_2SO_4 : max. at 308 and 521 mμ; log ε 4·04 and 4·19; min. at 290 and 392—406 mμ; log ε 3·97 and 3·75; infl. at 361—365 and 574—585 mμ; log ε 3·83, and 4·08. The infra-red spectrum showed max. at 731, 761, 852, 885, 921, 1031, 1062, 1104, 1205, 1232, 1259, 1287, 1339, 1408, 1587, 1621, and 3279 cm.$^{-1}$.

2 : 11-*Dihydroxy*-1-*piperidinoperylene*-3 : 10-*quinone* (VI).—The dihydroxy-quinone (100 mg.) readily dissolved in piperidine (10 c.c.), yielding a deep blue solution. After several days in contact with air, this solution, then deep purple, was poured into water and made just acid to litmus. The purple solid was collected, dried, and recrystallised several times from nitrobenzene, and the hygroscopic black-brown glistening crystals of 1-*piperidino*-2 : 11-*dihydroxy*-

perylene-3 : 10-*quinone* were well washed with methanol (Found in material dried at 140°/0·1 mm. for 20 hr. : N, 3·7. $C_{25}H_{19}O_4N$ requires N, 3·6%).

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Colouring Matters of the Aphididæ. Part X. Preparation and Properties of* 4 : 9-*Dihydroxyperylene*-3 : 10-*quinone.*

By A. CALDERBANK, A. W JOHNSON, and A. R. TODD.

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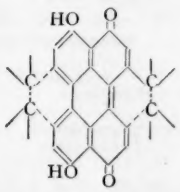
The compound described in the literature as perylene-3 : 4 : 9 : 10-diquinone has been shown to be 4 : 9-dihydroxyperylene-3 : 10-quinone. The similarity of the ultra-violet absorption spectrum of this compound to that of erythroaphin-*fb* confirms that this ring system is the chromophore of the aphin. Di*cyclo*hexylamino-, dipiperidino-, and tetrabromo-derivatives of the dihydroxyperylene-quinone have been prepared as well as 3 : 4 : 9 : 10-tetra-acetoxyperylene, the ultra-violet absorption spectrum of which closely resembles that of tetra-acetyldihydroerythroaphin-*fb*.

THE experiments described in Part IX* showed that perylene-3 : 10-quinone (I; R = H), like erythroaphin-*fb* (Part VII, *J.*, 1952, 4928), undergoes a variety of nucleophilic addition reactions. Thus *cyclo*hexylamine, piperidine, and sodium hydroxide in the presence of air gave 1-*cyclo*hexylamino-, 1-piperidino-, and 1-hydroxy-perylene-3 : 10-quinone respectively.

(I)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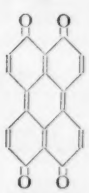
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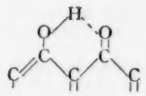
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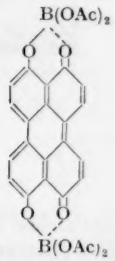
(V)

It was clearly desirable to investigate also the analogous reactions with the undescribed 4 : 9-dihydroxyperylene-3 : 10-quinone (I; R = OH) which resembles the proposed erythroaphin structure (II; Part VIII, *J.*, 1954, 107) even more closely. In 1929, Zinke, Hirsch, and Brozek (*Monatsh.*, **51**, 205; **52**, 13) obtained a compound which, they claimed, gave analyses for $C_{20}H_8O_4$, by the action of sulphuric acid at 150° on 3 : 4 : 9 : 10-tetrachloro-, 3 : 4 : 9 : 10-tetranitro-, 3 : 9-dichloro-4 : 10-dinitro-, or 3 : 10-dinitro-perylene. This product they formulated as perylene-3 : 4 : 9 : 10-diquinone (III). Reductive benzoylation gave 3 : 4 : 9 : 10-tetrabenzoyloxyperylene, oxidation with nitric acid gave mellitic acid, and the compound was stated to be insoluble in alkali. The marked stability of their product was a little surprising for a diquinone structure of this type. 1 : 4 : 5 : 8-Naphthadiquinone is rather unstable and is readily reduced to naphthazarin (Zahn and Ochwat, *Annalen*, 1928, **462**, 72, 86) and we have failed consistently to obtain the corresponding diquinone from erythroaphin, *e.g.*, on oxidation with lead tetra-acetate in glacial acetic acid. The preparation of Zinke's perylenediquinone by the action of sulphuric acid

* Part IX, preceding paper.

on 3 : 4 : 9 : 10-tetranitroperylene has therefore been repeated. A new pentanitroperylene has been isolated from the nitration products of perylene by Zinke and Unterkreuter's procedure (*Monatsh.*, 1919, **40**, 405) and a rather better yield of the tetranitro-compound has been obtained by modifying the strength of the nitric acid employed. The product isolated from the acid hydrolysis of tetranitroperylene gave analyses for $C_{20}H_{10}O_4$ and is 4 : 9-dihydroxyperylene-3 : 10-quinone (I; R = OH), and not the diquinone as Zinke believed. The dihydroxy-quinone, like erythroaphin, forms a very sparingly soluble greenish-blue sodium salt which probably led the earlier workers to think that the free quinone did not react with alkali. The sodium derivative is non-volatile, whereas the parent dihydroxy-quinone can be sublimed at 260—280°/10^{-4} mm.

The existence of a hydroxyl group in a *peri*-position to a quinone-carbonyl group causes the formation of a six-membered hydrogen-bonded ring (IV) which can be recognised by its effect on the infra-red spectrum (Flett, *J.*, 1948, 1441; Part V, Johnson, Quayle, Robinson, Sheppard, and Todd, *J.*, 1951, 2633). The intensity of the hydroxyl band is greatly

FIG. 1. FIG. 2.

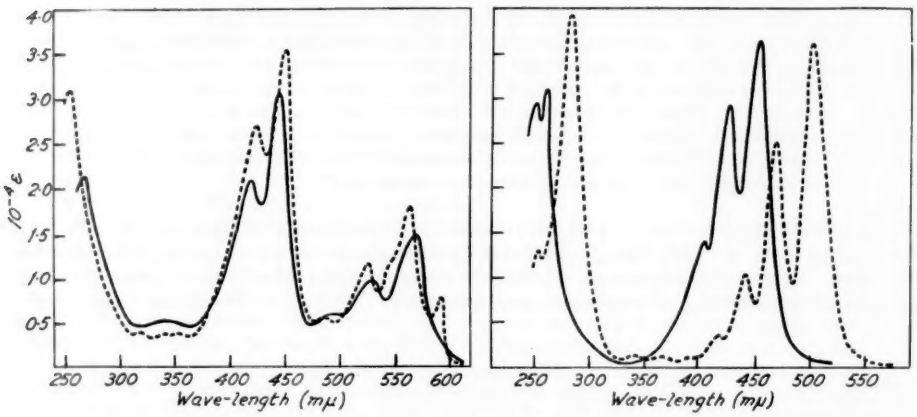

FIG. 1. *Ultra-violet absorption spectra of erythroaphin*-fb (– – – –) *and* 4 : 9-*dihydroxyperylene*-3 : 10-*quinone* (————) *in tetrachloroethane.*

FIG. 2. *Ultra-violet absorption spectra of tetra-acetyldihydroerythroaphin*-fb (– – – –) *and* 3 : 4 : 9 : 10-*tetra-acetoxyperylene* (————) *in chloroform.*

diminished if it appears at all, and the carbonyl band is displaced to longer wave-lengths. This phenomenon was noted in erythroaphin (Part V, *loc. cit.*) and it has also been observed with 4 : 9-dihydroxyperylene-3 : 10-quinone, which shows no hydroxyl band and has the main carbonyl band at 1631 cm.$^{-1}$ (cf. erythroaphin-*fb* at 1625 cm.$^{-1}$ and perylene-3 : 10-quinone at 1650 cm.$^{-1}$). Further, with boroacetate (cf. Dimroth and Faust, *Ber.*, 1921, **54**, 3020), 4 : 9-dihydroxyperylene-3 : 10-quinone gave a crystalline complex of structure (V). Hydrolysis regenerated the original quinone. A similar reaction with erythroaphin caused a marked change in the visible spectrum, similar to that observed with the dihydroxyperylenequinone, but the complex proved to be too unstable to be isolated in the crystalline state.

The close resemblance of the ultra-violet absorption spectrum of 4 : 9-dihydroxyperylene-3 : 10-quinone to that of erythroaphin-*fb* is so striking as to leave no further doubts as to the nature of the chromophore of the erythroaphin (Figs. 1 and 2).

Because of the sparing solubility of 4 : 9-dihydroxyperylene-3 : 10-quinone in common organic solvents, addition reactions, particularly addition of amines, have been carried out with a suspension of the quinone in pyridine. As with erythroaphin-*fb* (Part VII, *loc. cit.*), two mols. of *cyclo*hexylamine or piperidine were added to the quinone to give substituted diamino-4 : 9-dihydroxyperylene-3 : 10-quinones, dark microcrystalline solids which were

only sparingly soluble in hydrochloric acid. This was in contrast to the behaviour of perylene-3 : 10-quinone (Part IX), which formed only monoamino-adducts, the substitution occurring in the 1-position. From this evidence it is probable that in the 4 : 9-dihydroxyperylene-3 : 10-quinone series the amino-substituents occur in the 1 : 6- or 1 : 7-positions, thus emphasising the near-equivalence of the oxygen atoms in the *peri*-hydroxy-quinone system. Reaction of the dihydroxy-quinone with bromine gave a tetrabromo-derivative which was not orientated, although it should be noted that steric considerations would forbid the entry of bromines into both the 1- and the 12- (or 6- and 7-)positions.

Reductive acetylation of 4 : 9-dihydroxyperylene-3 : 10-quinone gave 3 : 4 : 9 : 10-tetra-acetoxyperylene, the ultra-violet absorption spectrum of which closely resembles that of tetra-acetyldihydroerythroaphin-*fb* (Part II, *J.*, 1950, 477) in general shape (Fig. 2). The displacement of the latter spectrum to longer wave-lengths is in accord with the presence of the additional nuclear substituents in the aphin derivative.

Experimental

3 : 4 : 9 : 10-*Tetranitroperylene.*—(*a*) Finely powdered perylene (4·0 g.) was nitrated with nitric acid (*d* 1·42; 280 c.c.) according to Zinke and Unterkreuter's method (*loc. cit.*). The insoluble portion of the reaction mixture was separated by filtration and washed and the combined filtrates were cooled; bright red needles of *pentanitroperylene* (0·47 g.) crystallised. These were recrystallised from nitrobenzene (5 c.c.), washed with boiling ethanol, and, for analysis, dried at 145°/0·2 mm. for 7 hr. (Found: C, 50·4, 50·1; H, 1·8, 2·0; N, 14·9. $C_{20}H_7O_{10}N_5$ requires C, 50·3; H, 1·5; N, 14·7%). The pentanitroperylene is sparingly soluble in chloroform but soluble in sulphuric acid, ethyl benzoate, or nitrobenzene, especially on warming. The absorption spectrum of a chloroform solution showed maxima at 322—323 and 480 mμ. The insoluble residue (3·76 g.) was powdered and stirred at 60—70° for 1 hr. with nitrobenzene (75 c.c.) in order to extract most of the remaining pentanitroperylene, which was precipitated from the filtrate by addition of ethanol (150 c.c.). The dried precipitate (487 mg.) was twice recrystallised from nitrobenzene, to give red needles of pentanitroperylene (266 mg.) (Found: N, 14·7%).

The residue (3·0 g.) was dissolved in boiling nitrobenzene (180 c.c.) as far as possible and the filtrate on cooling depositied red needles (1·38 g.) of 3 : 4 : 9 : 10-tetranitroperylene. For analysis, this was recrystallised from nitrobenzene, washed with boiling ethanol, and dried at 150°/0·15 mm. overnight (Found: C, 55·6; H, 1·9; N, 13·1. Calc. for $C_{20}H_8O_8N_4$: C, 55·5; H, 1·9; N, 13·0%). It formed a yellow-red solution in warm sulphuric acid and was soluble in 100 parts of boiling nitrobenzene and sparingly soluble in chloroform. The ultra-violet absorption spectrum of a chloroform solution showed maxima at 454 and 483 mμ.

(*b*) Finely powdered perylene (4·0 g.) was heated under reflux for 1 hr. with nitric acid (250 c.c.; *d* 1·39). After cooling, the red nitration product was separated, washed with nitric acid and water, dried (4·35 g.), and recrystallised from nitrobenzene (300 c.c.). The product, which formed small brick-red needles, was washed and dried (2·93 g.). For analysis it was again crystallised from nitrobenzene and was dried at 130°/0·15 mm. (Found: N, 13·1%).

4 : 9-*Dihydroxyperylene*-3 : 10-*quinone.*—3 : 4 : 9 : 10-Tetranitroperylene (1·36 g.) was heated with concentrated sulphuric acid (95 c.c.) at 130—140° for 6 hr. (cf. Zinke, Hirsch, and Brozek, *Monatsh.*, 1929, **51**, 205). After cooling and dilution, the deep red acid solution showed absorption in the visible region at 490, 536, and 578 mμ. The reaction product was added to water (1400 c.c.), and the flocculent brown precipitate separated on the centrifuge, washed, and then stirred with 10% sodium hydroxide solution (150 c.c.) for 10 min. The insoluble greenish sodium salt was separated (centrifuge) and suspended in more 10% sodium hydroxide solution (100 c.c.), and to the suspension sodium dithionite (5 g.) was added. The mixture was warmed on the steam-bath in an atmosphere of nitrogen until the quinone was completely reduced and the solution so obtained was quickly filtered through a thin layer of carbon. The reddish-brown vat, which showed a greenish fluorescence, was oxidised by bubbling air through the solution for 3 hr., and the greenish-blue precipitate which formed was separated on the centrifuge, washed, and dried (740 mg.). The product which was the sodium salt of the dihydroxyperylene-quinone was insoluble in nitrobenzene and did not sublime at 270°/10^{-4} mm. It was digested with warm dilute acid and the reddish-brown suspension separated, washed, and dried (550 mg.). After crystallisation of the product (100 mg.) from nitrobenzene (60 c.c.), very small, red,

solvated needles of 4 : 9-*dihydroxyperylene*-3 : 10-*quinone* (50 mg.) were obtained which were washed with boiling ethanol and dried at 150°/0·15 mm. for 12 hr. (Found: C, 74·7; H, 3·6; N, 2·4. $C_{20}H_{10}O_4,C_6H_5{\cdot}NO_2$ requires C, 71·3; H, 3·4; N, 3·2%). The product was then sublimed at 270—290°/10^{-4}—10^{-5} mm.; it formed black metallic needles (20 mg. in 24 hr.) (Found: C, 76·2; H, 3·2. $C_{20}H_{10}O_4$ requires C, 76·4; H, 3·2%). The product was soluble in 600 parts of boiling nitrobenzene and dissolved in concentrated sulphuric acid forming a pinkish red-fluorescent solution which showed bands in the visible spectrum at 490, 536, and 578 mμ (hand spectroscope). In *sym*-tetrachloroethane, the product showed absorption at 265—266, 340, 419, 444, 493, 526, and 567 mμ; log $\varepsilon_{max.}$ 4·33, 3·73, 4·32, 4·50, 3·77, 4·00, and 4·17 respectively (Fig. 1). The infra-red spectrum determined on a mull in Nujol showed maxima at 1631 (s), 1290 (s), 1242, 1186, 1145, 1072 (s), 926, 840, 787, and 673 cm.$^{-1}$.

3 : 4 : 9 : 10-*Tetra-acetoxyperylene*.—Anhydrous sodium acetate (200 mg.) and zinc dust (850 mg.) were added to a suspension of finely powdered 4 : 9-dihydroxyperylene-3 : 10-quinone in acetic anhydride (5 c.c.) and acetic acid (3 c.c.), and the mixture was vigorously stirred and heated under reflux for 20 min. After a few minutes the insoluble material dissolved to a reddish-brown solution but a precipitate was formed towards the end of the reaction. After cooling, excess of zinc was removed by decantation and the solid material in the product was separated, washed with cold dilute acetic acid and water, and dried (yield 375 mg.). It was easily soluble in hot nitrobenzene, moderately soluble in acetic anhydride, and sparingly soluble in xylene, carbon disulphide, and chloroform. Recrystallisation of a portion of the product (60 mg.) from nitrobenzene (5 c.c.) gave a *solvate* as reddish prisms (17 mg.) which were washed with boiling ethanol and dried at 135—150°/0·2 mm. for 16 hr. The product decomposed >350° (Found: C, 68·4; H, 4·5. $C_{28}H_{20}O_8,C_6H_5{\cdot}NO_2$ requires C, 68·3; H, 4·1%). The remainder of the crude product (315 mg.) was recrystallised from acetic anhydride (130 c.c.) and formed bronze-coloured leaflets (120 mg.) which were washed with acetic acid and then ethanol. After two further recrystallisations from ethyl benzoate (80 c.c. then 40 c.c.) *tetra-acetoxyperylene* was obtained as reddish-brown plates (40 mg.) (Found: C, 69·2; H, 4·4. $C_{28}H_{20}O_8$ requires C, 69·3; H, 4·1%). Light absorption in $CHCl_3$: max. at 251, 259, 403, 425, and 452 mμ; log ε 4·47, 4·49, 4·14, 4·47, and 4·56 respectively. The infra-red spectrum (Nujol mull) showed max. at 1764, 1600, 1408, 1302, 1208, 1186, 1131, 1039, 1014, 952, 946, 935, 893, 826, 800, and 746 cm.$^{-1}$.

Hydrolysis of 3 : 4 : 9 : 10-*Tetra-acetoxyperylene*.—The acetoxy-compound was suspended in 95% ethanol (7 c.c.), alcoholic sodium hydroxide (2 c.c.; 10%) was added, and the mixture heated under reflux for 15 min. Air was bubbled through the solution for 10 min. to complete the oxidation, and the insoluble sodium salt separated and washed. Acidification of an aqueous suspension of the salt with dilute acetic acid, as before, gave 4 : 9-dihydroxyperylene-3 : 10-quinone, which was purified by sublimation as described above (Found: C, 76·7; H, 3·5%).

4 : 9-*Dihydroxyperylene*-3 : 10-*quinone Bisboroacetate*.—A solution of boric acid (16 mg.) in acetic anhydride (3 c.c.) was added to a suspension of finely divided sublimed 3 : 10-dihydroxyperylene-4 : 9-quinone (16 mg.) in acetic anhydride (3 c.c.) at 60—70°. The mixture was kept at 100° for 30 min. with occasional shaking, the quinone slowly dissolving and a dark red crystalline complex separating from the hot solution. The *product* (21 mg.) was separated, washed with acetic anhydride and ether, and dried *in vacuo* at room temperature [Found: C, 59·1; H, 3·8; B, 3·9 (weighed as B_2O_3). $C_{28}H_{20}O_{12}B_2$ requires C, 59·0; H, 3·5; B, 3·8%]. The complex had no definite m. p. and was sparingly soluble in most organic solvents. A solution in acetic anhydride showed maxima in the visible spectrum (hand spectroscope) at 470, 538, and 583 mμ (cf. the visible spectrum of 4 : 9-dihydroxyperylene-3 : 10-quinone in acetic anhydride which shows bands at 445, 521, and 561 mμ). A solution of the boroacetate of erythroaphin-*sl* in acetic anhydride showed bands in the visible spectrum at 470, 537, and 582 mμ whereas the original quinone under similar conditions absorbed at 445, 518, and 559 mμ. Light absorption of 4 : 9-dihydroxyperylene-3 : 10-quinone bisboroacetate in $CHCl_3$: max. at 261, 416, 442, 470, 506, 530, 544, 570, and 588 mμ; log ε 4·58, 3·82, 4·30, 4·88, 3·49, 3·36, 4·00, 3·51, and 4·35 respectively. The infra-red spectrum, determined as a mull in Nujol, showed max. at 1715, 1701, 1631, 1575, 1531, 1427, 1389, 1316, 1294, 1274, 1198, 1103, 1075, 990, 962, 870, 855, 807, 794, 735, and 699 cm.$^{-1}$.

4 : 9-*Dihydroxydipiperidinoperylene*-3 : 10-*quinone*.—Redistilled piperidine (5 c.c.) was shaken with a suspension of finely powdered 4 : 9-dihydroxyperylene-3 : 10-quinone in dry pyridine (15 c.c.) at room temperature for one week. The solid slowly dissolved, forming a purple solution which was filtered and evaporated almost to dryness *in vacuo*. The residue was thoroughly extracted with chloroform (35 c.c.), the insoluble material (102 mg.; insoluble also

in 50% hydrochloric acid) separated, and the filtrate concentrated (to 5 c.c.) and diluted with hot 95% ethanol to precipitate the product. Next morning, the dark precipitate (90 mg.) was separated, washed with ethanol, and crystallised from pyridine–aqueous methanol. The *product* (42 mg.), which was an almost black granular solid, was separated, washed with hot water and methanol, and dried at 130°/0·4 mm. (Found : C, 74·7; H, 5·8; N, 5·4. $C_{30}H_{28}O_4N_2$ requires C, 75·0; H, 5·8; N, 5·8%). It was soluble in pyridine to a purple solution, sparingly soluble in chloroform, and not easily soluble in acids. Light absorption in $(CHCl_2)_2$: max. at 258—259, 430, 454, and 540—554 mμ; log ε 4·49, 4·09, 4·12, and 4·00 respectively. The infra-red spectrum (Nujol mull) showed max. at 3344, 1626, 1550, 1515, 1235, 1155, 1130, 1024, 990, 926, 862, 840, 807, 764, and 752 cm.$^{-1}$.

*Di*cyclo*hexylamino*-4 : 9-*dihydroxyperylene*-3 : 10-*quinone*.—A suspension of 4 : 9-dihydroxyperylene-3 : 10-quinone in dry pyridine (10 c.c.) and *cyclo*hexylamine (8 c.c.) was stirred at room temperature for 6 days. The green solution was then warmed on the steam-bath for 48 hr., during which time the colour changed to purple. The filtrate of the final mixture was evaporated almost to dryness under reduced pressure, and the residue dissolved in warm chloroform (15 c.c.) and again filtered. The chloroform solution was concentrated, diluted with hot 95% ethanol, boiled for 5 min., and then kept overnight. The black granular solid (213 mg.) was separated, washed, and dried, the purification from chloroform (10 c.c.)–ethanol was repeated, and the product (80 mg.) crystallised from pyridine–50% aqueous ethanol. For analysis the *di*cyclo*hexylamino*-compound was dried at 140°/0·5 mm. (Found : N, 5·5. $C_{32}H_{32}O_4N_2$ requires N, 5·5%). A solution in $CHCl_3$ showed max. at 264, 394—398, 440, 568, 576, and 588 mμ. The infra-red spectrum determined as a mull in Nujol showed max. at 3333, 1626, 1600, 1550, 1508, 1342, 1271, 1235, 1212, 890, 830, 820, and 754 cm.$^{-1}$.

Tetrabromo-4 : 9-*dihydroxyperylene*-3 : 10-*quinone*.—Finely powdered 4 : 9-dihydroxyperylene-3 : 10-quinone (250 mg.) was brominated according to Zinke, Hirsch, and Brozek's directions (*loc. cit.*). The dark-brown bromo-compound (100 mg.) was recrystallised from nitrobenzene, washed with hot ethanol, and finally recrystallised from ethyl benzoate (40 c.c.), to give dark maroon-coloured needles with a metallic lustre. These (62 mg.) were washed and dried at 150°/0·5 mm. for 12 hr. As a result of analysis (Found : C, 40·3; H, 1·7%), the sample was sublimed at 290—295°/5 × 10^{-5} mm., 10 mg. being obtained as short dark brown needles after 30 hr. (Found : C, 38·5; H, 1·0; Br, 50·7. Calc. for $C_{20}H_6O_4Br_4$: C, 38·1; H, 1·0; Br, 50·7%). Light absorption in $(CHCl_2)_2$: max. at 359, 450, 480, 534, and 576 mμ; log ε 3·80, 4·54, 4·73 4·12, and 4·22 respectively; infl. at 350—356 mμ; log ε 3·79.

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The Kinetics and Mechanisms of Aromatic Halogen Substitution. Part I. Acid-catalysed Chlorination by Aqueous Solutions of Hypochlorous Acid.

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In the presence of perchloric acid and silver perchlorate, the chlorination of anisole by *ca.* 0·001M-hypochlorous acid in aqueous solution appears to be a reaction of the kinetic form $-d[ClOH]/dt = k[ClOH] + k'[ClOH][H^+]$, the rate being almost independent of the concentration of aromatic compound over the range 0·004—0·01M. To achieve this kinetic form, the concentrations of chloride and of hypochlorite ions require to be reduced, by the presence of silver ions and of acid respectively, to insignificant levels. In aqueous dioxan, the rate is virtually the same as in water. By using, in the mixed solvent, higher concentrations of anisole, it can be shown that a term $k''[ClOH][H^+][ArH]$ enters into the kinetic expression. It is considered that the velocity coefficients k and k' give measures of the rates of heterolytic fission, to yield Cl^+, of ClOH and $ClOH_2^+$ respectively. The coefficient k'' gives a measure of the rate of attack of $ClOH_2^+$ on the aromatic compound. These conclusions are confirmed and amplified by investigation under similar conditions of the reactions of phenol, mesitylene, methyl *m*-tolyl ether, and methyl *p*-tolyl ether. Disturbances of the kinetics in the presence of anions X^- are discussed. The spontaneous decomposition of hypochlorous acid was negligibly slow under all the conditions investigated.

The kinetics of reactions in aqueous solution between hypochlorous acid and aromatic substances have not been studied extensively. For phenol in neutral and alkaline conditions Soper and Smith (*J.*, 1926, 1588) found kinetics consistent with a rate-determining reaction between un-ionised hypochlorous acid and the phenoxide ion. More recently, for the chlorination of sodium toluene-ω-sulphonate by hypochlorous acid in the presence of mineral acid Derbyshire and Waters (*J.*, 1951, 73) found the kinetic form $-d[ClOH]/dt = k[ArH][ClOH][H^+]$, involving either the chlorinium ion, Cl^+, or the hypochlorous acidium ion, $ClOH_2^+$.

Extensive investigations in these laboratories (cf. Hughes, Ingold, and Reed, *J.*, 1950, 2400) have shown that the nitronium ion, NO_2^+, rather than its hydrated form, the nitracidium ion ($H_2NO_3^+$), is frequently the electrophilic reagent involved in nitration. It is of interest to extend knowledge of aromatic substitutions by consideration of halogenation processes. The work of Bradfield and Jones and their co-workers (cf. Bradfield and Jones, *Trans. Faraday Soc.*, 1941, **37**, 726; Bradfield, Davies, and Long, *J.*, 1949, 1389) and of P. W. Robertson and his co-workers (cf. de la Mare and Robertson, *J.*, 1943, 279; Robertson, Dixon, Goodwin, McDonald, and Scaife, *J.*, 1949, 294), as also of Wilson and Soper (*J.*, 1949, 3376), demonstrates that molecular, rather than ionic, electrophilic reagents are of considerable importance when solutions of the halogens are allowed to react with aromatic substances. Our attention has been turned, therfore, to the reactions of hypochlorous acid; and an account of our preliminary investigations was given by de la Mare, Hughes, and Vernon (*Research*, 1950, **3**, 192). Neutral or alkaline conditions were avoided, since studies of the analogous electrophilic addition reactions have revealed extremely complicated kinetic forms (cf. Israel, *J.*, 1950, 1286). The intervention of chlorine, through the reaction $ClOH + H^+ + Cl^- \rightleftharpoons Cl_2 + H_2O$, was prevented by the addition of sufficient silver perchlorate to reduce the significance of this equilibrium to negligible proportions. In order to increase the range of concentration of aromatic compound available for investigation, aqueous dioxan was in some cases used as solvent.

Experimental

(a) *Materials and Methods.*—To purify commercial mercuric oxide, it was dissolved in perchloric acid and precipitated by the addition of sodium hydroxide. After repetition of this process, the product was washed with much hot distilled water. Hypochlorous acid was

prepared by shaking a solution of chlorine in water with excess of purified mercuric oxide. The product was distilled *in vacuo* at about 35° in the dark, and stored over purified mercuric oxide for not more than 5 days, during which time the rate of reaction with anisole under standard conditions remained unaltered. Bulk samples of hypochlorous acid prepared in this way were usually about 0·05M.

The following organic substances were purified by fractional distillation of good commercial specimens: anisole, b. p., 153·8°/763 mm., n_D^{25} 1·5149; mesitylene, b. p., 162°/760 mm., n_D^{25} 1·4958; methyl *m*-tolyl ether, b. p. 174°/763 mm., n_D^{25} 1·5070; methyl *p*-tolyl ether (reactive impurities first removed by partial bromination), b. p. 176°/758 mm., n_D^{25} 1·5094. *p*-Dimethoxybenzene on recrystallisation had m. p. 57·5°; toluene-*p*-sulphonic acid had m. p. 104°; and phenol, after distillation, had m. p. 40°.

Solutions of these substances were made up by weight, in water or in mixtures of water and dioxan. The latter solvent was first refluxed with hydrochloric acid in a current of nitrogen for 6 hr., and was then partially dried with solid sodium hydroxide. Peroxide impurities were then removed by shaking with ferrous sulphate, and the product was distilled from solid sodium hydroxide in an atmosphere of nitrogen and was stored under nitrogen in the dark. Such material was completely inert to hypochlorous acid under the conditions of the rate measurements.

Solutions of silver perchlorate were prepared by shaking excess of freshly precipitated silver oxide with perchloric acid. The product was filtered, and its silver content was estimated in conventional manner. It was neutral in reaction. Other reagents were of analytical grade.

For rate measurements, the reagents (usually *ca.* 250 ml.), except the hypochlorous acid, were brought to the temperature of the thermostat in a darkened bottle. Hypochlorous acid (usually *ca.* 3 ml.), previously warmed to the temperature of the thermostat, was added, the mixture was shaken, and at appropriate intervals, portions (usually 10 or 25 ml.) were pipetted into flasks containing excess of ice-cold aqueous potassium iodide solution (500 g./l., sufficient to dissolve the precipitate of silver iodide), this solution and the titration vessel having previously been flushed with nitrogen. The liberated iodine was then titrated with *ca.* 0·003N-sodium thiosulphate solution, sodium starch glycollate or starch being used as indicator.

In early experiments, erratic results were obtained when the hypochlorous acid was prepared from unpurified mercuric oxide. It is believed that the lack of reproducibility was caused by the presence of nitrite ions, which were detected colorimetrically in water which had been kept over unpurified mercuric oxide (cf. Winkler, *Report Pharm.*, 1829, **31**, 475). Added mercuric perchlorate (10^{-6}—10^{-3}M) had no effect on the rate of reaction between anisole and acidified hypochlorous acid. Carefully redistilled hypochlorous acid reacted with anisole, in the presence of added mineral acid and silver perchlorate, at the same rate as similar samples which had been kept either over mercuric oxide (our usual practice) or over bismuth hydroxide (cf. Israel, Martin, and Soper, *J.*, 1950, 1282). Spontaneous decomposition of the hypochlorous acid was shown by blank experiments to be negligibly slow, even in the presence of silver ions, added mineral acid, and dioxan.

(b) *Rate Measurements for the Chlorination of Anisole in Aqueous Solution (at 25° except where otherwise specified).*—The following are details of a typical experiment, with 0·0099M-anisole, 0·0006M-hypochlorous acid, 0·012M-perchloric acid, and 0·013M-silver perchlorate; 10-ml. portions were titrated with 0·0033N-sodium thiosulphate.

Time (min.)	0·00	10·25	19·00	26·75	38·75	47·50	68·00
Titre (ml.)	4·52	4·14	3·82	3·60	3·25	2·99	2·55
10^2k_1 (min.$^{-1}$) *	—	0·86	0·86	0·85	0·85	0·87	0·84

* All values of k_1 quoted in this paper are in these units, and have been calculated by the formula $k_1 = 2{\cdot}303\ [\log_{10}(a_0/a_t)]/t$, where a_t is the titre at time t minutes.

The following results show the variation in rate coefficient with the concentration of added silver perchlorate, for the reaction between 0·0066M-anisole and 0·0005M-hypochlorous acid, catalysed by 0·0090M-perchloric acid.

$[Ag^+]$ (M)	0·0064	0·013	0·033	0·13
10^2k_1 (min.$^{-1}$)	0·71	0·66	0·65	0·67

Similar results were obtained at other concentrations of acid. It appears to require, at this concentration of anisole, somewhat more than 0·006M-silver ion to reduce the concentration of chloride ion to insignificance; at concentrations of silver ion greater than this, the rate coefficient for the chlorination is substantially constant.

The following are results obtained when the initial concentration of hypochlorous acid was varied; they refer to the chlorination of 0·0066M-anisole in the presence of 0·013M-silver perchlorate, catalysed by 0·60M-perchloric acid.

[HOCl] (M)	0·0010	0·0005	0·0002
10^2k_1 (min.$^{-1}$)	8·5	7·6	7·8

Similar results were obtained at lower concentrations of acid; hence, the dependence of the rate on the acidity and on the concentration of the aromatic compound being temporarily neglected, the kinetic form for the reaction, over the concentration range given, is $-d[ClOH]/dt \propto [ClOH]$.

The following are results for the chlorination of anisole by 0·0005M-hypochlorous acid, in the presence of 0·013M-silver perchlorate, catalysed by 0·012M-perchloric acid, showing the very small dependence of the rate on the concentration of anisole:

Anisole (M)	0·0099	0·0088	0·0066	0·0055	0·0033
10^2k_1 (min.$^{-1}$)	0·85	0·88	0·89	0·83	0·87

In aqueous dioxan, the rate of reaction, other conditions being the same, was found to be almost identical with that in water, and the former solvent was therefore used to extend the range of concentration of anisole available for investigation. The following are results for the chlorination of anisole by hypochlorous acid in the presence of 0·065M-silver perchlorate, with 0·050N-perchloric acid as catalyst:

Anisole (M)	0·008	0·015	0·019	0·028
10^2k_1 (min.$^{-1}$)	1·41	1·59	1·78	1·95

Other results * are plotted in Figs. 1 and 2, and show that the dependence of the rate on the concentration of anisole, though small, is quite definite under these conditions.

The following results show the temperature-dependence of the rate of chlorination of 0·0066M-anisole by 0·0007M-hypochlorous acid, in the presence of 0·16M-silver perchlorate, with 0·012M-perchloric acid as catalyst:

Temp.	0·0°	24·7°	35·0°
10^2k_1 (min.$^{-1}$)	0·30	0·93	1·65

(c) *Product of Chlorination of Anisole.*—To an aqueous solution (25 l., containing 0·0055M-anisole, 0·05M-silver perchlorate, and 0·12M-perchloric acid), there were added, at intervals of 3 hr. or more, twelve portions, each 200 ml., of 0·07M-hypochlorous acid. The product was then extracted with ether, and the ethereal extract was dried ($CaCl_2$) and fractionated, giving 16·0 g. (82%), n_D^{25} 1·5377, b. p. 198—201°, m. p. *ca.* −50° (Found: C, 58·4; H, 4·8; Cl, 25·2. Calc. for C_7H_7OCl: C, 59·0; H, 4·9; Cl, 24·9%). These properties are those of a mixture of *o*-chloroanisole, n_D^{25} 1·5433, f. p. −26·5°, and *p*-chloroanisole, n_D^{25} 1·5338, f. p. −18·0°.

Since Dr. Lars Melander (personal communication) had kindly informed us that some *p*-benzoquinone can be isolated from the reaction of *p*-dimethoxybenzene with acidified hypochlorous acid,† the following experiment was carried out. Anisole (0·0049M) was allowed to react to completion with 0·0006M-hypochlorous acid in the presence of 0·013M-perchloric acid and 0·016M-silver perchlorate. The resulting solution was filtered, and the optical density was compared with that of water at various wave-lengths, in 0·2-cm. silica cells, with a Unicam model S.P. 500 spectrophotometer. The absorption curve for anisole passes through a maximum at 2750 Å, and through a minimum at 2450 Å. That for *p*-benzoquinone passes through a maximum ($\varepsilon = 17{,}700$) at 2420 Å (Braude, *J.*, 1945, 490). The solutions both of anisole and of chlorinated anisole had similar absorption curves, passing through minima in the neighbourhood of 2450 Å, at which wave-length the optical densities were respectively 0·28 and 0·22. *p*-Benzoquinone is therefore not formed in the reaction of hypochlorous acid with anisole. In a separate experiment, it was found that a negligible amount of demethylation occurs during the chlorination, since very little phenolic material can be extracted by alkali from the crude product of the reaction.

* At high concentrations of aromatic compounds, a larger concentration of silver ion was found necessary in order to reach a region in which the rate was independent of the silver-, and therefore of the chloride-ion concentration. This may be the result of complex-formation between the aromatic compound and silver ion (cf. Andrews and Keefer, *J. Amer. Chem. Soc.*, 1950, **72**, 3313). The results in the Figures all refer to conditions under which further addition of silver ion did not significantly affect the rate.

† For this reason, the reaction of *p*-dimethoxybenzene with hypochlorous acid has not been further investigated, though we have confirmed that the initial rate of disappearance of hypochlorous acid is nearly the same as for anisole.

(d) *Kinetics of Chlorination of Other Aromatic Substances.*—Results similar to those obtained for anisole were obtained for phenol; for the reaction of 0·0037M-phenol with 0·0003M-hypochlorous acid, in the presence of 0·0204N-silver perchlorate and 0·012M-perchloric acid, 10^2k_1 was very consistently 0·86.

Similarly, for the chlorination of 0·0027M-phenol by 0·0005M-hypochlorous acid, in the presence of 0·06M-silver perchlorate and 0·60M-perchloric acid, consistent values for 10^2k_1 (average 9·2; range 8·7—9·8) show that the reaction at high concentrations of acid is still of first order with respect to hypochlorous acid.

The dependence of the rate on the concentration of silver ions, and of acid, was in every way

Chlorination by hypochlorous acid (< 0·001M) in 50% aqueous dioxan at 25° in the presence of 0·065M-silver perchlorate.

FIG. 1. $HClO_4$, 0·012M.

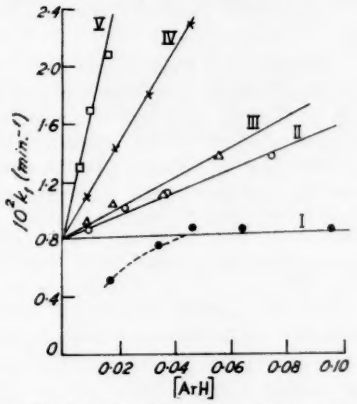
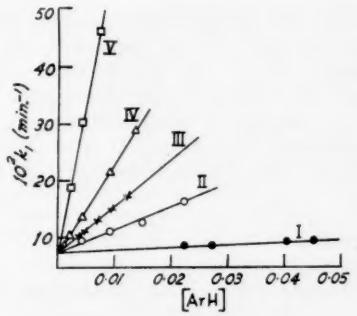


FIG. 2. $HClO_4$, 0·60M.



I = methyl *p*-tolyl ether; II = anisole; III = mesitylene; IV = phenol (in water: $Ag^+ = 0·15$M); V = methyl *m*-tolyl ether.

similar to that obtained with anisole. Thus the following are data for the chlorination of 0·0092M-phenol by 0·0005M-hypochlorous acid in the presence of 0·012M-perchloric acid:

$[Ag^+]$ (M)	0·008	0·016	0·040	0·080	0·16
10^2k_1 (min.$^{-1}$)	1·36	1·14	1·16	1·09	1·09

The dependence of the rate on the concentration of aromatic compound, and of acid, is shown for mesitylene, methyl *p*-tolyl ether, and phenol by the following data for chlorinations catalysed by 0·050N-perchloric acid: *

Methyl *p*-tolyl ether (M)	0·052	0·065	0·078	—
10^2k_1 (min.$^{-1}$; $Ag^+ = 0·027$M)	1·17	1·12	1·20	—
Phenol * (M)	0·002	0·006	0·0098	0·018
10^2k_1 (min.$^{-1}$; $Ag^+ = 0·027$M)	1·37	2·20	2·65	4·01
Mesitylene (M)	0·013	0·025	0·035	—
10^2k_1 (min.$^{-1}$; $Ag^+ = 0·065$M)	1·92	2·59	3·22	—

For all these compounds, the individual kinetic runs showed that the reactions were of the first order with respect to hypochlorous acid. The Figures show similar results at other acidities, including data for methyl *m*-tolyl ether.

(e) *Product of Chlorination of Phenol.*—To an aqueous solution (22 l., containing 0·106M-phenol, 0·05M-silver perchlorate, and 0·12M-perchloric acid) there were added, at intervals of 3 hr. or more, 25 batches, each containing 200 ml. of *ca.* 0·06M-hypochlorous acid. The product was extracted with ether, and, after removal of most of the ether, the mixed chlorophenols were methylated with methyl sulphate and alkali. The product was made acid and extracted with ether; the ethereal extract was dried and fractionated, giving 25·3 g. of mixed chloroanisoles (76%), b. p. 198—201°, n_D^{25} 1·5370, m. p. *ca.* −49° (Found: C, 59·6; H, 5·0; Cl, 25·4. Calc. for C_7H_7OCl: C, 59·0; H, 4·9; Cl, 24·9%).

(f) *Kinetics of Chlorination of Anisole in the Presence of Added Anions.*—The following

* Here, and also in Figs. 1 and 2, the values for phenol are for aqueous solution, and those for other compounds are for 50% dioxan–water.

results are for the chlorination of 0·0077—0·0099M-anisole by *ca.* 0·0005M-hypochlorous acid in the presence of 0·013M-silver perchlorate and 0·012M-perchloric acid:

Catalyst	None	ClO_4^- 2·2M	*p*-$C_6H_4Me{\cdot}SO_3^-$ 0·012M	*p*-$C_6H_4Me{\cdot}SO_3^-$ 1·0M	SO_4^{--} 0·0002M	SO_4^{--} 0·006M	SO_4^{--} 0·03M
10^2k_1 (min.$^{-1}$)	0·85	1·33	0·72	2·2	1·14	1·33	1·69

The following results for the chlorination of 0·0077M-anisole by high concentrations of hypochlorous acid, in the presence of 0·013M-silver perchlorate and 0·012M-perchloric acid, illustrate that, at concentrations of hypochlorous acid greater than about 0·001M, the rate of reaction becomes partly proportional to the square of the concentration of hypochlorous acid; a similar result is found if mineral acid is omitted from the chlorinating mixture, so that the pure kinetic form, $v \propto [HOCl]$, is no longer obtained.

[HOCl] (M)	0·0005	0·0010	0·0020	0·0030	0·0060	0·012
10^2k_1	0·86	0·98	1·61	2·52	4·21	6·37

Discussion

In our preliminary communication (de la Mare, Hughes, and Vernon, *loc. cit.*), it was recorded that the reaction between hypochlorous acid and anisole, in the presence of silver perchlorate, was of the kinetic form $-d[ClOH]/dt \propto [ClOH]$, and that the velocity coefficient was dependent on the acidity, and was independent of the concentration of aromatic compound, being the same for anisole (0·003—0·01M), phenol (0·003—0·008M), and *p*-dimethoxybenzene. It was concluded that the measured rate was that of the heterolytic fission of ClOH and $ClOH_2^+$, the reactions involved being shown in the scheme below:

$$ClOH \underset{b}{\overset{a}{\rightleftharpoons}} Cl^+ + OH^- \quad . . . . . (1)$$

$$ClOH + H^+ \underset{d}{\overset{c}{\rightleftharpoons}} ClOH_2^+ \quad . . . . . (2)$$

$$\overset{+}{Cl}OH_2 \underset{f}{\overset{e}{\rightleftharpoons}} Cl^+ + OH_2 \quad . . . . . (3)$$

$$Cl^+ + ArH \xrightarrow[g]{} ArCl + H^+ \quad . . . . . (4)$$

The conditions of reaction used in this preliminary study were such that the kinetics were not quite of pure form, being generally of an order slightly greater than unity with respect to hypochlorous acid. In the present investigation, this complication was eliminated by the use of concentrations of hypochlorous acid less than 0·001M.

The results illustrated in Figs. 1 and 2 accord in every detail with the requirements of equations (1)—(4). For the less reactive substances, such as methyl *p*-tolyl ether and anisole, the rate of reaction is only slightly dependent on the concentration of aromatic compound, this dependence being only detectable with certainty when the concentration of aromatic compound attainable in solution is increased by the addition of dioxan to the aqueous solvent. For all the compounds, at a given concentration of acid, the plot of first-order velocity coefficient, calculated with respect to the disappearance of hypochlorous acid, extrapolates back, within experimental error, to the same point. This extrapolated value, which is independent of the nature of the compound, and therefore must refer to some characteristic of the hypochlorous acid, depends on the concentration of hydrogen ion, as is illustrated by the following values:

$[H^+]$ (M)	0·000	0·012	0·050	0·60
10^2k_1 (min.$^{-1}$, found)	—	0·82	1·10	5·0
10^2k_1 [min.$^{-1}$, calc. from eqn. (5)]	(0·75)	0·84	1·10	5·0

The rate of reaction approximates, therefore, at small concentrations of aromatic compound, to the expression:

$$-d[ClOH]/dt = k[ClOH] + k'[ClOH][H^+] \quad . . . . . (5)$$

where $10^2k = 0{\cdot}75$ min.$^{-1}$, $10^2k' = 7{\cdot}1$ l. mole^{-1} min.$^{-1}$. It is considered that these terms are best interpreted as representing the rates of heterolytic fission respectively of ClOH and $ClOH_2^+$.

A consequence of the proposed mechanism is that, if the concentration of aromatic

compound is sufficiently reduced, a point should eventually be reached at which the aromatic compound is unable successfully to compete with the reassociation of Cl^+ and OH^-, or of Cl^+ and H_2O. Just as in the analogous case of nitration, therefore, the rate of reaction should begin to decrease with decreasing concentration of aromatic compound, and this decrease should have its onset at lower values of the concentration of aromatic compound the more reactive this compound. In full agreement with these expectations, a falling-off in rate is observed, for phenol, at *ca.* 0·0015M; for anisole, at *ca.* 0·005M; and for methyl *p*-tolyl ether, at *ca.* 0·05M, as is shown for the last compound by the broken line in Fig. 1. No extensive investigation of this behaviour has been made, since Derbyshire and Waters (*loc. cit.*) examined carefully the chlorination of the toluene-ω-sulphonate ion, which is considerably less reactive than methyl *p*-tolyl ether, and observed the limiting kinetic form $-d[ClOH]/dt \propto [ArH][ClOH][H^+]$.

An alternative trial explanation of the observation that the reaction, although dependent on the concentration of aromatic compound, provided this is sufficiently low, becomes independent of it above a critical concentration of aromatic compound, is that the reaction rate, above the critical concentration, is determined by the slow transfer of a proton to the hypochlorous acid.* Such a hypothesis would mean, however, that there could be operative under these conditions only one chlorinating agent (namely, H_2OCl^+), which could give a range of concentration of aromatic compound over which the kinetic form, $-d[ClOH]/dt = k[ArH][ClOH][H^+]$, could be observed. The scheme of equations (1)—(4), however, allows the presence in the solution of two chlorinating species, Cl^+ and $ClOH_2^+$; and the possibility then exists that a sufficiently reactive aromatic compound may react with the latter cation directly, without waiting for the formation of the chlorinium ion, Cl^+. Our proposed mechanism (in contrast with the above slow-proton-transfer hypothesis) allows, therefore, that the kinetic equation for the reaction may contain a term proportional to $[ClOH][H^+][ArH]$, even above the critical concentration of aromatic compound, so that the kinetic equation in these circumstances becomes :

$$-d[ClOH]/dt = k[ClOH] + k'[ClOH][H^+] + k''[ClOH][H^+][ArH] \quad . \quad . \quad . \quad . \quad (6)$$

Figs. 1 and 2, in which the full lines refer to concentrations greater than the critical value, show that the results require the inclusion of all these terms.† Thus the plots of velocity coefficient against the concentration of aromatic compound are linear, with positive slopes dependent on the nature of the compound. The following table shows that these slopes are dependent on the acidity.

Dependence of first-order velocity coefficients on the concentration of aromatic compound.

	Slope (s, l. mole^{-1} min.$^{-1}$) of graph of 10^2k_1–[ArH]			$10^{-2}s/[H^+] = k''$, l.^{2} mole^{-2} min.$^{-1}$		
Compound	$[H^+]$ = 0·012	$[H^+]$ = 0·050	$[H^+]$ = 0·60	$[H^+]$ = 0·012	$[H^+]$ = 0·050	$[H^+]$ = 0·60
Methyl *p*-tolyl ether	0·5	1·25	40	0·4	0·5	0·7
Anisole	7·8	33	394	6·5	6·5	6·6
Mesitylene	10·3	63	800	8·6	12·6	13·3
Phenol	32·5	163	1530	27·1	32·6	25·5
Methyl *m*-tolyl ether	89	—	5000	74	—	83

For methyl *p*-tolyl ether, the dependence of the rate of reaction on the concentration of aromatic compound is so small that it cannot accurately be determined from the graphs.

* Such a hypothesis does not allow for the inclusion in the kinetic expression of a term dependent only on the concentration of hypochlorous acid; this term can only be explained on the basis of a slow change in the latter substance, as is most reasonably ascribed to the breaking of the Cl–O bond (cf. de la Mare, Hughes, and Vernon, *loc. cit.*).

† At concentrations below the critical concentration, the rate is limited, not by the rate of fission of ClOH and $ClOH_2^+$, but by the reactivity of the aromatic compound. Hence the rate expression, $-d[ClOH]/dt \propto [ClOH][H^+][ArH]$ is observed; the proportionality factor includes a small contribution from k''. In principle, there should still be a contribution also from a term in the rate expression, $-d[ClOH]/dt \propto [ClOH][ArH]$; but this would be very difficult to observe experimentally, since at concentrations sufficiently below the critical value for the observations of a pure kinetic form, that fraction of the rate dependent on this term would be very small, and would probably even be obscured by the spontaneous decomposition of hypochlorous acid. To obtain a measurable rate with the toluene-ω-sulphonate ion, for example, Derbyshire and Waters (*loc. cit.*) worked at concentrations of aromatic compound *ca.* 0·03M, and of perchloric acid in the range 2—4M.

In the case of the other four compounds, the near constancy in the values of k'' shown in the last three columns of the Table show that the increase in reaction velocity with concentration of aromatic compound is directly dependent on the acidity. Hence, above the critical concentration of aromatic compound, the kinetic equation (6) satisfactorily represents the results, and we may conclude that the rate is not, under our conditions, controlled by the rate of a proton-transfer to the oxygen of the hypochlorous acid molecule.

The reactions of cations with anions are usually rather rapid. Hence such reactions as are shown by equations (7) and (8) might readily be expected to compete with those of the aromatic compound with the hypochlorous acidium and chlorinium ions:

$$ClOH_2^+ + Cl^- \longrightarrow Cl_2 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$ClOH_2^+ + OCl^- \longrightarrow Cl{\cdot}OCl + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

The importance of Cl_2 and of Cl_2O as chlorinating agents has often been stressed (cf. Shilov, Kupinskaya, and Yasnikow, *Doklady Akad. Nauk S.S.S.R.*, 1951, **81**, 435; Shilov and Kupinskaya, *ibid.*, p. 621; Israel, Martin, and Soper, *J.*, 1950, 1282; Reeve and Israel, *J.*, 1952, 2327). Hence it is not at all surprising that chlorination of anisole by hypochlorous acid is more rapid in the absence of silver ions. It appears to be necessary to reduce the concentration of Cl^- to below about 10^{-9}M in order to suppress completely any reaction through molecular chlorine.

In a similar way, it may be calculated from the acidic dissociation constant of HOCl ($K = 3 \times 10^{-8}$ at 20°; Shilov, *J. Amer. Chem. Soc.*, 1938, **60**, 490) that the concentration of hypochlorite ion must be reduced, by the presence of acid, to below about 10^{-6}N to eliminate completely the reaction route through Cl_2O. If mineral acid is not added at all to the reaction medium, or if the concentration of hypochlorous acid is allowed to exceed about 0·001M, the reaction begins to depend on the square of the concentration of hypochlorous acid, as was shown on p. 1294.

It may, in fact, be stated as a general rule that any anion X^-, provided its nucleophilic power is appreciable, will combine with the hypochlorous acidium ion or the chlorinium ion to form a chlorinating entity ClX:

$$ClOH_2^+ + X^- \longrightarrow ClX + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

There are many reports in the literature concerning the existence of such chlorinating agents (cf., *e.g.*, Shilov and his co-workers, *locc. cit.*; Soper, Israel, and their co-workers, *locc. cit.*; Derbyshire and Waters, *loc. cit.*). In the present work, it has been recorded that the ions Cl^-, OCl^-, HSO_4^-, p-$C_6H_4Me{\cdot}SO_3^-$, and ClO_4^- fall in decreasing order of effectiveness in catalysing the reaction in this way, the perchlorate ion in particular having very little effect, even at high concentrations.

Since the formation of ClX by such a route may or may not be rate-determining, and seeing also that ClX may be formed directly from ClOH, it can be seen that the presence of such an anion in a solution in which ClOH is acting as a chlorinating agent may introduce kinetic terms proportional to $[ClOH][X^-]$, $[ClOH][X^-][H^+]$, $[ClOH][X^-][ArH]$, and $[ClOH][X^-][H^+][ArH]$. Shilov (*Doklady Akad. Nauk S.S.S.R.*, 1952, **84**, 1001; cf. *Chem. Abs.*, 1952, **46**, 9958) has stated that the conclusions proposed as result of our preliminary investigation (de la Mare, Hughes, and Vernon, *loc. cit.*) are inconsistent with his work. His conclusions apply, however, to conditions of low acidity and of high concentration of hypochlorous acid, and often also to experiments in which other anions were present. Our conclusions are in no way inconsistent with his, seeing that in our work we have gone to considerable trouble to eliminate the disturbances of this sort. The specific criticism that our results are vitiated by the addition of silver salts because these accelerate the decomposition of hypochlorous acid has been shown repeatedly in the course of this investigation to be inapplicable; blank determinations have shown that such a decomposition is of negligible rate in comparison with the reactions under investigation.

In nitration, it has been found possible to distinguish kinetically between nitration by the nitronium ion, NO_2^+, and by the nitracidium ion $H_2NO_3^+$. The present results show that a similar kinetic distinction can be drawn between the chlorinium ion, Cl^+, and the hypochlorous acidium ion, $ClOH_2^+$. Ingold ("Structure and Mechanism in Organic

Chemistry," Bell and Sons, London, 1953, p. 293) has recently discussed, and made plausible theoretically on the basis of a suggestion due to D. J. Millen, that there should be an energy barrier between these ions in aqueous solution, despite the fact that one is merely the hydrate of the other. The observation of a slow rate-determining reaction of ClOH and of $ClOH_2^+$, in each case giving an electrophilic reagent more powerful than its precursor, is in our opinion best interpreted as in equations (1)—(4), though other possibilities are consistent with the observed kinetics. Thus Professor R. S. Mulliken (personal communication) has put forward the view that these slow reactions might be the isomerisations :

$$Cl\text{–}O\text{–}H \longrightarrow H\text{–}Cl{=}O \; (\longleftrightarrow H\text{–}Cl^{+}\text{–}O^{-}) \quad . \; . \; . \; . \; . \; . \; . \quad (10)$$

$$Cl\text{–}OH_2^{+} \longrightarrow H\text{–}Cl{=}\overset{+}{O}\text{–}H \; (\longleftrightarrow H\text{–}Cl^{+}\text{–}O\text{–}H) \quad . \; . \; . \; . \; . \; . \quad (11)$$

We prefer our formulation, on the grounds that such entities as $H\text{–}Cl{=}\overset{+}{O}\text{–}H$ would not be expected to be particularly good chlorinating agents. Thus attack by the latter ion on an aromatic compound requires in the transition state that a proton and a hydroxide ion be lost from the electrophilic chlorine in a single process, whereas the hypochlorous acidium ion can attack and chlorinate by the splitting of a single bond, releasing a water molecule to the solvent.

We are greatly indebted to Professor E. D. Hughes, F.R.S., for the suggestion which led to the inception of this investigation, as also to him and to Professor C. K. Ingold, F.R.S., for many valuable discussions. We are happy to acknowledge technical assistance from Mr. E. Grayson. Analyses are partly by Mr. A. V. Winter of this Department.

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Preparation of Aromatic Aldehydes and Ketones from Diazonium Salts.

By W. F. Beech.

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A new method for preparing aromatic aldehydes and alkyl aryl ketones is described. Diazonium salts react with formaldoxime, acetaldoxime, propionaldoxime, and acetaldehyde semicarbazone severally, under carefully controlled conditions, to give arylated derivatives which can be hydrolysed to aromatic aldehydes or ketones.

o-Nitrobenzaldehyde can be conveniently prepared in this way from *o*-nitroaniline in 33% yield.

The reaction between diazonium salts and hydroxyiminoacetone according to the equation :

$$Ar{\cdot}N_2Cl + CH_3{\cdot}CO{\cdot}CH{:}N{\cdot}OH \xrightarrow{\text{Aq. NaOH}} CH_3{\cdot}CO{\cdot}CAr{:}N{\cdot}OH + N_2 + HCl$$

discovered by Borsche (*Ber.*, 1907, **40**, 737) suggested that oximes of simpler constitution might behave similarly and so provide a new and convenient method for preparing aromatic aldehydes and ketones from amines :

$$Ar{\cdot}NH_2 \longrightarrow Ar{\cdot}N_2Cl \longrightarrow ArRC{:}N{\cdot}OH \longrightarrow Ar{\cdot}COR$$

Apart from a brief reference to the reaction between diazonium salts and formaldoxime in I.G. Farbenindustrie research reports (FD. 2729/46, B.I.O.S./DOCS/1156/1121), no mention is made in the literature of the use of simple oximes such as formaldoxime, acetaldoxime, and the like in this type of reaction. On investigation, however, many diazonium salts were found to react readily with formaldoxime, acetaldoxime, and propionaldoxime in this sense. It was also shown that acetaldehyde semicarbazone is arylated by certain diazonium salts similarly.

The yields of arylated oximes, and hence of aldehydes and ketones, obtained by this

method vary considerably according to the conditions. More favourable results were obtained with slightly acid (pH 5·5—6·0) than with the alkaline media employed by Borsche (*loc. cit.*). In acid conditions, however, a catalyst was generally essential, a cupric sulphate–sodium sulphite mixture (cf. Philipp, *Annalen*, 1936, **523**, 285) being satisfactory. The function of the sulphite in conjunction with cupric sulphate is not clear, but in some condensations it appears to accelerate the reaction more than does cupric sulphate alone, and to lead to rather higher yields. If too high a concentration of sulphite is used, however, the yield falls; 0·032 mol. of sulphite per mol. of diazonium salt was about the optimum.

The effect of varying the molecular ratio of cupric sulphate to diazonium salt was investigated for condensations of *p*-chloro- and *o*-nitro-benzenediazonium chlorides with formaldoxime. Other factors being equal, the yield of aldehyde obtained on subsequent hydrolysis was a maximum when 0·1—0·2 mol. of cupric sulphate per mol. of diazonium salt was present. Some typical results are given in Table 1. In some cases, similar yields

TABLE 1. *Effect of varying the ratio, cupric sulphate : diazo-compound, on the yield of aldehyde obtained* (0·032 *mol. of sodium sulphite*).

R in $R{\cdot}C_6H_4{\cdot}N_2Cl$:	*p*-Cl				*o*-NO_2		
Proportion of cupric sulphate (mol.) ...	0·02	0·1	0·2	0·5	0·1	0·2	0·3
Yield of aldehyde (%)	48	60	57	35	20	33	25

were obtained with cuprous chloride, but use of nickel sulphate reduced them by about one-half. As diazonium chlorides frequently yield chlorohydrocarbons in the presence of copper salts, experiments were made in which chloride ions were completely excluded. Condensation of *p*-chlorobenzenediazonium sulphate with formaldoxime, however, gave only 43% of aldehyde, *o*-nitrobenzenediazonium sulphate only 21%.

The optimum pH range (5·5—6·0) for the reaction between diazonium salts and formaldoxime was conveniently obtained by working in aqueous media strongly buffered with sodium acetate. Lower yields resulted when sodium carbonate (pH 9·5—10·0), sodium hydrogen carbonate (pH 8·0—8·5) or calcium carbonate (pH 6·5—6·8) was used to regulate the pH.

In order to investigate the scope of the reaction, a number of aromatic aldehydes were prepared from amines, the diazonium salts being condensed with formaldoxime under the conditions described. The resulting arylaldoximes were converted into the corresponding aldehydes by acid hydrolysis or by treatment with boiling aqueous ferric ammonium sulphate (cf. Gabriel and Meyer, *Ber.*, 1881, **14**, 2336). The overall yields (amine to aldehyde) obtained are given in Table 2. The yields of arylated oximes were commonly

TABLE 2. *Yields of aldehydes obtained from amines.*

Aldehyde	Yield (%)	Aldehyde	Yield (%)
Benzaldehyde	40	*o*-Methoxybenzaldehyde	34
o-Tolualdehyde	46	*p*-Anisaldehyde	42
m-Tolualdehyde	41	2-Naphthaldehyde	25
p-Tolualdehyde	46	*p*-Ethoxycarbonylbenzaldehyde	20
o-Chlorobenzaldehyde	52	Pyridine-3-aldehyde	14
m-Chlorobenzaldehyde	50	Diphenyl-2-aldehyde	Very poor
p-Chlorobenzaldehyde	60	Diphenyl-4 : 4′-dialdehyde	
o-Nitrobenzaldehyde	33	Di-*p*-formylphenyl ether	
Salicylaldehyde	9		

higher than those yields of aldehydes, dehydration of some aldoximes to nitriles occurring as a side-reaction during hydrolysis with boiling dilute mineral acids (cf. Hantzsch and Lucas, *Ber.*, 1895, **28**, 746). Control experiments established that the yield of *p*-chlorobenzaldoxime from *p*-chlorobenzenediazonium chloride and formaldoxime under optimum conditions was *ca.* 75%, the yield of *p*-chlorobenzaldehyde being some 15% lower.

The diazo–formaldoxime reaction failed to give the expected aldehyde when certain *o*-substituted diazonium chlorides were used. Thus, although satisfactory results were obtained with *o*-methyl-, *o*-halogeno-, and *o*-nitro-benzenediazonium salts, none of the required aldehyde was isolated when *o*-cyano- or *o*-ethoxycarbonyl groups were present.

The use of formaldoxime with an unsubstituted hydroxyl group appears to be essential to the reaction, for *O*-substituted derivatives, *e.g.*, *O*-methylformaldoxime, failed to give any simple product on treatment with *p*-chlorobenzenediazonium chloride.

Condensation of diazonium salts with acetaldoxime, acetaldehyde semicarbazone, or propionaldoxime and subsequent hydrolysis gave alkyl aryl ketones in somewhat lower yields. The diazo–acetaldoxime reaction is especially useful for the synthesis of certain substituted acetophenones which are otherwise difficult of access, such as 4-acetylphthalic acid which was conveniently prepared by use of methyl 4-aminophthalate.

In order to test the scope of the reaction, the ketones shown in Table 3 were prepared.

TABLE 3.

Ketone	Yield (%)	Ketone	Yield (%)
o-Chloroacetophenone	43	*p*-Diacetylbenzene	33
p-Chloroacetophenone	35—45	1 : 3-Diacetyl-4-chlorobenzene	15
p-Chloropropiophenone	30	4-Acetylphthalic acid	27
m-Diacetylbenzene	27		

Synthesis of arylated oximes by the diazo-reaction was often accompanied by formation of by-products arising by replacement of the diazo-group by hydrogen. This was very noticeable when preparing 1 : 3-diacetyl-4-chlorobenzene and pyridine-3-aldehyde.

No *p*-chlorobenzophenone oxime was isolated from *p*-chlorobenzendiazonium chloride and benzaldoxime, indicating that further reaction of diazo-compound with the aromatic aldoxime cannot be responsible for limitation of yield in the reaction with formaldoxime.

The method for preparing aldehydes and ketones described above succeeds only to a limited extent with difunctional compounds. Condensation of tetrazotised *p*-phenylenediamine with acetaldoxime and subsequent hydrolysis gave less than 10% of *p*-diacetylbenzene, while attempts to prepare aromatic diketones from diazonium salts and dialdoximes such as glyoxime and succindialdoxime were unsuccessful.

EXPERIMENTAL

Preparation of Aliphatic Aldoximes.—Formaldoxime. As this substance polymerises very readily (Scholl, *Ber.*, 1891, **24**, 573; Dunstan and Bossi, *J.*, 1898, **73**, 353), it was prepared and used as required in dilute aqueous solution without isolation. A 10% solution for use in conjunction with 0·25 mole of diazonium salt was made by heating paraformaldehyde (11·5 g.) with hydroxylamine hydrochloride (26·3 g.) in water (170 c.c.) until a clear solution was obtained, adding hydrated sodium acetate (51 g.), and boiling gently under reflux for 15 min. In cases where the diazonium sulphate was used in the subsequent condensation, hydroxylamine hydrochloride was replaced by an equivalent amount of the sulphate.

Acetaldoxime was prepared by Wieland's method (*Ber.*, 1907, **40**, 1677).

Propionaldoxime. Hydroxylamine hydrochloride (87·5 g.) in water (85 c.c.) was treated with sodium carbonate (69 g.) in water (250 c.c.), and the solution was kept at 5—10° while propaldehyde (72·5 g.) was added gradually. After 2 hr., the oxime was extracted with ether (400 c.c.) and dried ($MgSO_4$). Fractional distillation through a 4″ gauze-packed column yielded propionaldoxime (70 g., 77%), b. p. 130—132°.

General Procedure for Preparing Aldehydes from Amines.—(i) p-*Chlorobenzaldehyde from* p-*chloroaniline.* A solution of *p*-chlorobenzenediazonium chloride, prepared from *p*-chloroaniline (32 g.), hydrochloric acid (57 c.c.; *d* 1·18), water (50 c.c.), and ice (100 g.) by treatment with sodium nitrite (17·5 g.) in water (25 c.c.) at 0—5°, was made neutral towards Congo-red by addition of hydrated sodium acetate (22 g.) in water (35 c.c.). The neutral diazonium solution was introduced below the surface of 10% aqueous formaldoxime, to which had been added copper sulphate (6·25 g.), sodium sulphite (1·0 g.; anhyd.), and further sodium acetate (165 g.) in water (180 c.c.), at 10—15° with stirring. Stirring was then continued for 1 hr. The mixture (*ca.* 1000 c.c.) was rendered acid to Congo-red with hydrochloric acid and, after addition of a further quantity (230 c.c.; *d* 1·18) of this acid, was boiled under reflux for 2 hr. After distillation of the *p*-chlorobenzaldehyde in steam, the distillate (1000—1500 c.c.) was neutralised with sodium hydrogen carbonate, and the aldehyde was extracted with ether (750 c.c.). The crude product obtained by distilling off the ether was shaken with aqueous sodium hydrogen sulphite (90 c.c.; 40%) at 60°, water (275 c.c.) was added, and non-aldehydic material was removed by extraction with ether (90 c.c.). After regeneration from the aqueous layer by boiling sulphuric acid (45 c.c.; *d* 1·84) and water (45 c.c.) for 0·5 hr., the aldehyde was removed in ether (300 c.c.).

The ethereal solution was dried ($MgSO_4$) and evaporated, and the residue was distilled, giving *p*-chlorobenzaldehyde (21 g., 60%), m. p. 48°, b. p. 98°/14 mm. The semicarbazone had m. p. 233° (Found: N, 21·75; Cl, 18·0. Calc. for $C_8H_8ON_3Cl$: N, 21·25; Cl, 17·95%). To estimate the losses occurring during purification, *p*-chlorobenzaldoxime (19·45 g.) was boiled under reflux for 2 hr. with 2N-hydrochloric acid. The product of hydrolysis was distilled in steam and further purified as previously, giving *p*-chlorobenzaldehyde (13·75 g., 78%).

(ii) o-*Nitrobenzaldehyde from* o-*nitroaniline*. A solution of *o*-nitrobenzenediazonium chloride, prepared from *o*-nitroaniline (34·5 g.), hydrochloric acid (57 c.c.; *d* 1·18), water (50 c.c.), and ice (100 g.) by treatment with sodium nitrite (17·5 g.) in water (25 c.c.) at 0—2°, was made neutral towards Congo-red by addition of hydrated sodium acetate (22 g.) in water (35 c.c.). The neutral diazonium solution was introduced below the surface of a 10% aqueous formaldoxime solution, to which had been added copper sulphate (12·5 g.), sodium sulphite (1·0 g.; anhyd.) and further sodium acetate (165 g.) in water (180 c.c.), at 10—15° with stirring. Stirring was then continued for 1 hr. The mixture was rendered acid to Congo-red with hydrochloric acid, and the liquor was decanted from the crude, tarry oxime which was then boiled under reflux with ferric ammonium sulphate (300 g.) in water (500 c.c.) for 1 hr. The crude aldehyde (20 g.), which was isolated by steam-distillation, extraction of the distillate (*ca.* 1500 c.c.) with ether (750 c.c.), and subsequent distillation of the ether, was shaken with aqueous sodium hydrogen sulphite (50 c.c.; 40%), and water (100 c.c.) at 50° was added. After removal of non-aldehydic material by extraction of the cooled solution with ether (80 c.c.), the aldehyde was regenerated by treatment of the aqueous solution with sufficient 10N-sodium hydroxide to render it faintly alkaline to Clayton-yellow. The product was then removed in ether (300 c.c.) and dried ($MgSO_4$) and the solvent removed by distillation, finally under reduced pressure. The residue consisted of almost pure *o*-nitrobenzaldehyde (12·3 g., 33%), m. p. 43—44°, characterised by formation of indigo with warm acetone and dilute aqueous sodium hydroxide.

(iii) *Other aromatic aldehydes*. The remaining aldehydes listed in Table 2 were prepared similarly, with copper sulphate (12·5 g.) and sodium sulphite (1·0 g.; anhyd.) as catalyst for 0·25-mole preparations. The aldehydes were characterised as the derivatives shown in Table 4,

TABLE 4. *Derivatives prepared for characterisation.*

Aldehyde, or R in R·C_6H_4·CHO	Derivative	M. p. of deriv.	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
H	Phenylhydrazone	158°	—	—	—	—	—	—
o-Me	Phenylhydrazone, $C_{14}H_{14}N_2$	105—106	79·5	6·9	12·9	80·0	6·65	13·3
m-Me	Semicarbazone, $C_9H_{11}ON_3$	216—217	—	—	23·75	—	—	23·7
p-Me	Phenylhydrazone, $C_{14}H_{14}N_2$	114	—	—	13·0	—	—	13·3
o-Cl	α-*Oxime* *	74	—	—	—	—	—	—
m-Cl	Phenylhydrazone, $C_{13}H_{11}N_2Cl$	134	—	—	11·9	—	—	12·15
p-MeO	Semicarbazone	210—211	—	—	—	—	—	—
p-CO_2Et	Phenylhydrazone, $C_{16}H_{16}O_2N_2$	142—143	71·95	6·0	10·6	71·65	5·95	10·45
2-Naphthaldehyde	Phenylhydrazone	206	—	—	—	—	—	—
Pyridine-3-aldehyde	Phenylhydrazone, $C_{12}H_{11}N_3$	157—158	72·7	5·65	21·65	73·1	5·6	21·3
Diphenyl-2-aldehyde	Semicarbazone, $C_{14}H_{13}ON_3$	208—209	70·2	5·2	17·9	70·3	5·45	17·55
Di-*p*-formylphenyl ether	Dianil, $C_{26}H_{20}ON_2$	155	82·85	5·45	7·4	83·0	5·3	7·45

* Found: Cl, 22·85. C_7H_6ONCl requires Cl, 22·85%.

identities being established either by mixed m. p., or by analysis where no authentic sample was available. *p*-Ethoxycarbonylbenzaldehyde was prepared from ethyl *p*-aminobenzoate as described for *o*-nitrobenzaldehyde. After the oxime had been boiled with aqueous ferric ammonium sulphate, however, the aldehyde was extracted with chloroform. The crude aldehyde was purified through the bisulphite compound as with *o*-nitrobenzaldehyde. Subsequent distillation under reduced pressure gave *p*-ethoxycarbonylbenzaldehyde as a liquid, b. p. 142—144°/15 mm.

Pyridine-3-aldehyde.—A diazonium solution, prepared from 3-aminopyridine (23·5 g.), hydrochloric acid (68 c.c.; *d* 1·18), sodium nitrite (17·5 g.), and water (75 c.c.), was condensed with 10% aqueous formaldoxime in the presence of an excess of sodium acetate in the usual manner. The mixture was then made slightly acid to Congo-red with hydrochloric acid, a solution of

ferric chloride (150 g.; anhyd.) in water (150 c.c.) was added and the solution was boiled under reflux for 1 hr. Sodium carbonate was then added in slight excess and the aldehyde was distilled in steam. The distillate (*ca.* 1500 c.c.) was treated with hydrochloric acid (50 c.c.; *d* 1·18), after which it was concentrated to 30 c.c. under reduced pressure. The concentrated solution was saturated with potassium carbonate, the aldehyde was extracted with chloroform (150 c.c.), and the chloroform solution dried (K_2CO_3). After distillation of the chloroform, pyridine-3-aldehyde (3·6 g., 14%) was distilled under reduced pressure, having b. p. 95—100°/16 mm. (Harries and Lenárt, *Annalen*, 1915, **410**, 115 give b. p. 95—97°/15 mm.).

*Diphenyl-2-aldehyde and Di-*p*-formylphenyl Ether.*—Prepared in the usual manner from 2-aminodiphenyl and 4 : 4′-diaminodiphenyl ether respectively, these aldehydes were obtained in poor yields in the form of derivatives. Likewise, from benzidine was obtained a very poor yield of a substance, m. p. 140°. Ullmann and Loewenthal (*Annalen*, 1904, **332**, 76) give m. p. 145° for diphenyl-4 : 4′-dialdehyde.

Preparation of Ketones from Amines.—p-*Chloroacetophenone.* (*a*) A diazonium solution, prepared from *p*-chloroaniline (32 g.) and neutralised with sodium acetate as previously described, was condensed with a solution of acetaldoxime (22·5 g.) in water (200 c.c.) containing copper sulphate (12·5 g.), sodium sulphite (1·0 g.; anhyd.), and sodium acetate (165 g.) at 10—15° as described for aldehydes. After acidification (Congo-red) with hydrochloric acid and addition of a further quantity (230 c.c.; *d* 1·18), the mixture was boiled under reflux for 3 hr. and the ketone was distilled in steam. After extraction of the neutralised distillate with ether (750 c.c.) and recovery, the ketone was purified through its derivative with Girard T reagent. Regeneration, followed by distillation under reduced pressure, gave *p*-chloroacetophenone (13·75 g., 36%), b. p. 101°/9 mm. The semicarbazone had m. p. 202—203° (Found : N, 19·8. Calc. for $C_9H_{10}ON_3Cl$: N, 19·85%).

Purification through the derivative with Girard T reagent may in other cases often be replaced with advantage by fractional distillation through a metal-packed column. In this manner, *o*-chloroacetophenone, b. p. 104—105°/15 mm., was prepared in 43% yield from *o*-chloroaniline.

(*b*) A hot solution of acetaldehyde semicarbazone (38 g.) in water (200 c.c.) was poured into a solution of sodium acetate (136 g.) in water (140 c.c.) with stirring. After addition of copper sulphate (12·5 g.) and sodium sulphite (1·0 g.; anhyd.) and cooling to 10°, a diazonium solution, prepared from *p*-chloroaniline (32 g.) and neutralised by sodium acetate (51 g.) in water (75 c.c.), was introduced below the surface at 10—20°. When the vigorous evolution of nitrogen had subsided, *p*-chloroacetophenone semicarbazone, m. p. 187—189° was isolated by filtration. After one recrystallisation from ethanol, it (20·6 g., 40%) had m. p. 196°. By hydrolysis of the crude product with boiling 2N-hydrochloric acid and purification as above, *p*-chloroacetophenone was obtained in 40—45% overall yield.

p-*Diacetylbenzene.*—(*a*) *p*-Aminoacetophenone (33·8 g.) was diazotised at 0° in sulphuric acid (17 c.c.; *d* 1·84) and water (200 c.c.) by addition of sodium nitrite (17·5 g.) in water (25 c.c.). The diazonium solution, after neutralisation with sodium acetate (22 g.) in water (35 c.c.), was condensed with acetaldoxime (22·5 g.) in water (180 c.c.) containing copper sulphate (12·5 g.), sodium sulphite (1·0 g.; anhyd.), and sodium acetate (165 g.) at 10—15°. The crude, tarry oxime was separated and boiled under reflux with 2N-sulphuric acid (500 c.c.) for 2 hr. The crude *p*-diacetylbenzene, after extraction with chloroform (600 c.c.) and recovery, was distilled in superheated (170°) steam. The product was removed from the distillate by chloroform-extraction and was, after recovery, purified by crystallisation from light petroleum (b. p. 100—120°), giving *p*-diacetylbenzene (13·5 g., 33%), m. p. 106°, raised to 113° by one further crystallisation (Ingle, *Ber.*, 1894, **27**, 2527, gives m. p. 114°).

(*b*) *p*-Phenylenediamine (13·5 g.) was added gradually to a mixture of sulphuric acid (45 g., 100%), water (22 c.c.), and nitrososulphuric acid (66 g., 50% solution in sulphuric acid), the temperature being kept at 20—25°. The tetrazonium salt was precipitated when the solution was poured on ice (75 g.) and the whole cooled to −15° to −20°. After isolation by filtration, the salt was suspended in ice-water and the suspension was made neutral to Congo-red by sodium acetate, then added to a solution of acetaldoxime (22·5 g.) in water (140 c.c.) containing sodium acetate (136 g.), copper sulphate (12·5 g.), and sodium sulphite (1·0 g.; anhyd.) during 0·5 hr. at 10—15°. After hydrolysis of the crude oxime with boiling 2N-hydrochloric acid, extraction with chloroform, and recovery, the product was distilled under reduced pressure. The slightly moist crystals (2·1 g.) thus obtained had m. p. and mixed m. p. 113—114° after recrystallisation from light petroleum (b. p. 100—120°).

m-Diacetylbenzene was prepared from *m*-aminoacetophenone by the method (*a*). Its dioxime

had m. p. 206° (Ruggli and Staub, *Helv. Chim. Acta*, 1936, **19**, 972, give m. p. 204°) (Found: C, 62·3; H, 5·9; N, 14·2. Calc. for $C_{10}H_{12}O_2N_2$: C, 62·5; H, 6·25; N, 14·6%).

1 : 3-*Diacetyl*-4-*chlorobenzene* was similarly obtained in rather poor yield from 3-amino-4-chloroacetophenone. Recrystallised from *cyclo*hexane, it had m. p. 54° (Found: C, 60·7; H, 4·5; Cl, 17·95. $C_{10}H_9O_2Cl$ requires C, 61·05; H, 4·6; Cl, 18·05%). A considerable amount of *p*-chloroacetophenone was obtained as by-product.

4-*Acetylphthalic Acid.*—A diazonium solution (300 c.c.) prepared from dimethyl 4-aminophthalate (52·75 g.) and neutralised by addition of sodium acetate was condensed with an aqueous solution of acetaldoxime (22·5 g.) containing copper sulphate (12·5 g.), sodium sulphite (1·0 g.; anhyd.), and excess of sodium acetate in the usual manner. The liquor was decanted from the crude oxime which was boiled under reflux for 2 hr. with ferric ammonium sulphate (300 g.) in water (500 c.c.). The crude keto-ester was extracted with chloroform (750 c.c.) and, after drying, the product was recovered and fractionally distilled; the fraction, b. p. 180—200°/15 mm., was collected. The keto-ester was hydrolysed for 4 hr. with boiling 11N-sodium hydroxide (50 c.c.), water (50 c.c.), and ethanol (50 c.c.). After removal of the ethanol and addition of water (50 c.c.), the solution was treated with hydrochloric acid (*d* 1·18) until only a faint alkalinity remained, then clarified with carbon, and further hydrochloric acid was added to give a strong acidity towards Congo-red. 4-Acetylphthalic acid (13·1 g.) separated at 0°. A further 0·9 g. of product was obtained by evaporating the filtrate to dryness and extracting the residue with boiling methanol. The crude product (14 g., 27%) had m. p. 196—200° (decomp.), raised to 210° (decomp.) by crystallisation from acetic acid (Found: C, 57·3; H, 3·95. Calc. for $C_{10}H_8O_5$: C, 57·7; H, 3·85%). [Mayer, Stark, and Schön, *Ber.*, 1932, **65**, 1336, give m. p. 210—211° (decomp.).]

p-Chloropropiophenone, prepared from *p*-chloroaniline as described for *p*-chloroacetophenone, propaldoxime being used in place of acetaldoxime, melted at 35° and formed a *semicarbazone*, m. p. 178° (Found: N, 18·85. $C_{10}H_{12}ON_3Cl$ requires N, 18·6%) (Collet, *Compt. rend.*, 1898, **126**, 1577, gives m. p. 35—36° for the ketone).

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Steroids. Part XIII. The Conversion of Ergosterol into Progesterone.*

By Francis Johnson, G. T. Newbold, and F. S. Spring.

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The conversion of ergosterol into 3β-hydroxypregnan-20-one is described, thus completing a route from the yeast sterol to progesterone (cf. *Chem. and Ind.*, 1953, 1230).

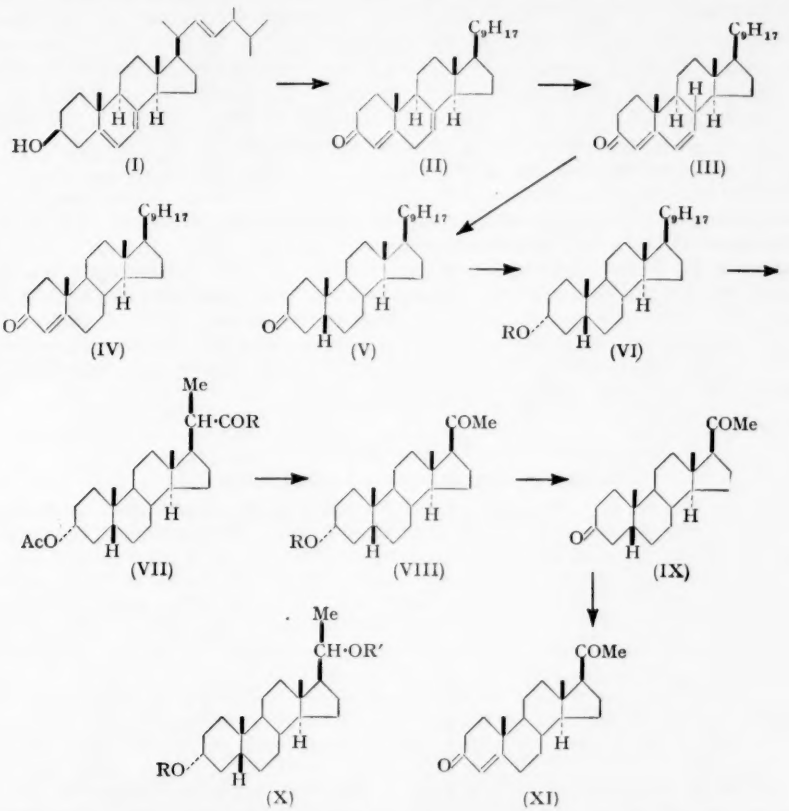
Microbiological oxidation of progesterone (XI) gives 11α-hydroxyprogesterone (Peterson, Murray, Eppstein, Reineke, Weintraub, Meister, and Leigh, *J. Amer. Chem. Soc.*, 1952, **74**, 5933) which can be transformed into cortisone by a ten-step route of high overall efficiency (Mancera, Ringold, Djerassi, Rosenkranz, and Sondheimer, *ibid.*, 1953, **75**, 1286). The limited availability of progesterone led us to explore the possibility of employing ergosterol (I) as a starting material for its partial synthesis.

Oxidation of ergosterol to ergosterone (II) by the Oppenauer method (*Rec. Trav. chim.*, 1937, **56**, 137) gave a highly coloured product requiring extensive purification. A considerable improvement was made by using aluminium *tert.*-butoxide in toluene with *cyclo*hexanone as hydrogen acceptor. The method of Barton, Cox, and Holness (*J.*, 1949, 1771) was used for the rearrangement of (II) to *iso*ergosterone (ergosta-4 : 6 : 22-trien-3-one) (III). Selective hydrogenation of *iso*ergosterone, with a palladium catalyst in the presence of alkali, gave 5β-ergost-22-en-3-one (V) in high yield.

Reduction of *iso*ergosterone (III) to ergosta-4 : 22-dien-3-one (IV) was also accomplished by partial hydrogenation in the presence of a palladium catalyst in benzene. Reduction

* Part XII, *J.*, 1954, 1223.

of Δ^8-11-oxo-steroids with lithium in liquid ammonia gives the corresponding saturated-11-oxo-steroid (Turnbull, Chamberlin, Reinhold, Erickson, Ruyle, Chemerda, and Tishler, *J. Amer. Chem. Soc.*, **1952**, **74**, 2696; Sondheimer, Yashin, Rosenkranz, and Djerassi, *ibid.*, p. 2696), whereas with excess of lithium in liquid ammonia in the presence of methanol the saturated 11α-hydroxy-steroid is obtained (Sondheimer *et al.*, *loc. cit.*). More recently Barton, Ives, and Thomas (*Chem. and Ind.*, 1953, 1180) found that reduction of Δ^4-3-oxo-steroids with lithium in liquid ammonia leads to the saturated 5α-ketones. We find that reduction of the conjugated dienone (III) with excess of lithium in liquid ammonia in the presence of methanol gives ergosta-4 : 22-dien-3-one (IV) in good yield. Hydrogenation of this in the presence of palladium in an alkaline medium also gives 5β-ergost-22-en-3-one (V). When (V) is crystallised from methanol containing a trace of mineral acid, it readily



forms a ketal from which the parent ketone is re-formed by hydrolysis with aqueous mineral acid.

Reduction of 5β-ergost-22-en-3-one with lithium aluminium hydride, followed by acetylation, gives 5β-ergost-22-en-3α-yl acetate (VI; R = Ac) in good yield, and hydrolysis then gives 5β-ergost-22-en-3α-ol (VI; R = H); the last compound has been prepared by Barton, Cox, and Holness (*loc. cit.*) by sodium–propanol reduction of 5β-ergost-22-en-3-one (V) which they obtained together with (IV) by careful fractionation of the complex mixture obtained by partial hydrogenation of *iso*ergosterone (III) in presence of platinum in ethyl acetate.

Ozonolysis of 5β-ergost-22-en-3α-yl acetate (VI; R = Ac) in chloroform at −45° and decomposition of the ozonide with zinc dust and acetic acid gave a mixture of 3α-acetoxy-

bisnorcholan-22-al (VII; R = H) and 2 : 3-dimethylbutyraldehyde, and each was characterised as its 2 : 4-dinitrophenylhydrazone. The aldehyde (VII; R = H) was further characterised and identified by oxidation to 3α-acetoxybisnorcholanic acid (VII; R = OH) which had previously been obtained by side-chain degradation of lithocholic acid (Reindel and Niederlander, *Ber.*, 1935, **68**, 1969; Sawlewicz and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 949).

Treatment of 3α-acetoxybisnorcholan-22-al (VII; R = H) with acetic anhydride and potassium acetate gave an oily enol acetate, ozonolysis of which, followed by decomposition with zinc dust and acetic acid, gave 20-oxopregnan-3α-yl acetate (VIII; R = Ac) as major product; hydrolysis yielded the alcohol (VIII; R = H). The last compound has been prepared from lithocholic acid (Meystre and Miescher, *Helv. Chim. Acta*, 1946, **29**, 33) and also from pregnane-3 : 20-dione (IX) by preferential reduction either catalytically (Marker, Kamm and Wittle, *J. Amer. Chem. Soc.*, 1937, **59**, 1841; Butenandt and Müller, *ibid.*, 1938, **71**, 191) or with sodium borohydride (Mancera *et al.*, *loc. cit.*). A second, amorphous (minor) product from the ozonolysis of the enol-acetate was readily separated by chromatography, being much more strongly held by alumina. On acetylation it yielded 3α : 20α-diacetoxypregnane (X; R = R′ = Ac). The isolation of this diacetate is attributed to the formation of a small quantity of 3α-acetoxypregnan-20α-ol (X; R = Ac, R′ = H) during the zinc treatment of the ozonolysis product. The diol (X; R = R′ = H) has been isolated from pregnancy urine by Hartman and Locher (*Helv. Chim. Acta*, 1935, **18**, 160) and has been obtained by sodium and *iso*propyl alcohol reduction of 3α-hydroxypregnan-20-one (VIII; R = H) (Butenandt and Müller, *loc. cit.*).

Oxidation of 3α-hydroxypregnan-20-one (VIII; R = H) yielded pregnane-3 : 20-dione (IX) (Marker and Kamn, *J. Amer. Chem. Soc.*, 1937, **59**, 1373) from which progesterone (XI) may be obtained by Butenandt and Schmidt's method (*Ber.*, 1934, **67**, 1901).

Since this work was completed, similar partial syntheses of progesterone from ergosterol have been briefly described by the Upjohn group (*Chem. Eng. News.*, 1953, 3977) and Daglish, Green, and Poole (*Chem. and Ind.*, 1953, 1207).

Experimental

For general instructions see *J.*, 1954, 1219, 1224.

Ergosterone (*Ergosta*-4 : 7 : 22-*trien*-3-*one*).—A solution of ergosterol (50 g.) in dry toluene (500 c.c.) and *cyclo*hexanone (375 g.) was distilled until 50 c.c. of distillate had been collected. A solution of freshly prepared aluminium *tert.*-butoxide (50 g.) in dry toluene (400 c.c.) was then added rapidly and the solution heated under reflux for 2 hr. The cooled mixture was washed with sulphuric acid (4 × 1000 c.c.; 4%), water, 10% aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue heated at 138—140°/10^{-4} mm. to remove self-condensation products of *cyclo*hexanone; neglect of this precaution caused a marked reduction of the yield. The residue, crystallised from acetone–light petroleum (b. p. 60—80°), gave ergosterone (40·5 g.) as pale yellow needles, m. p. 123—126°, which was used for the next stage without further purification. A specimen, twice recrystallised from the same solvent, yielded ergosterone, m. p. 134°, $[\alpha]_D$ −12° (*c*, 4·5) (Found: C, 84·8; H, 10·5. Calc. for $C_{28}H_{42}O$: C, 85·2; H, 10·7%). Light absorption: Max. at 2400 Å (ε 13,300). It gives a yellow colour with tetranitromethane in chloroform. Oppenauer (*loc. cit.*) gives m. p. 131·5—132°, $[\alpha]_D$ −15·7°; Heilbron, Kennedy, Spring, and Swain (*J.*, 1938, 869) give m. p. 132°, $[\alpha]_D$ −0·8°; Wetter and Dimroth (*Ber.*, 1937, **70**, 1665) give m. p. 132°, $[\alpha]_D$ −0·5°, −0·8°.

iso*Ergosterone* (*Ergosta*-4 : 6 : 22-*trien*-3-*one*).—Ergosterone (16 g.) in dry chloroform (150 c.c.) was treated with a stream of dry hydrogen chloride at 0° for 1 hr. The red solution was washed with water, 10% aqueous potassium carbonate, and water, and dried (Na_2SO_4). Recrystallisation of the product from ethyl acetate–methanol yielded *iso*ergosterone, m. p. 100° (14·5 g.), which was used for the next stage. A sample twice crystallised from the same solvent separated as thick rods, m. p. 106—107°, $[\alpha]_D$ −24·5° (*c*, 1·0) (Found: C, 84·9; H, 10·9%). Light absorption: Max. at 2840 Å (ε = 28,000). It gives a pale yellow colour with tetranitromethane in chloroform. Heilbron, Kennedy, Spring, and Swain (*loc. cit.*) give m. p. 108°, $[\alpha]_D$ −30°; Wetter and Dimroth (*loc. cit.*) give m. p. 110°; Barton, Cox, and Holness (*loc. cit.*) give m. p. 105°.

Ergosta-4 : 22-*dien*-3-*one*.—(*a*) *iso*Ergosterone (0·5 g.) in thiophen-free benzene (20 c.c.) was shaken with a suspension of palladised strontium carbonate (2%; 0·25 g.) in benzene (10 c.c.) under hydrogen for 45 min.; absorption then approximated to 1 mol. The product was crystallised from aqueous acetone, to yield ergosta-4 : 22-dien-3-one (0·2 g.) as needles, m. p. 129—130°, $[\alpha]_D$ +42° (*c*, 1·4) (Found : C, 84·9; H, 11·3. Calc. for $C_{28}H_{44}O$: C, 84·8; H, 11·2%). Light absorption : Max. at 2400 Å (ε 18,700). It gives a pale yellow colour with tetranitromethane in chloroform. Barton, Cox, and Holness (*loc. cit.*) give m. p. 127·5—128·5°, $[\alpha]_D$ +43°, +44°.

(*b*) *iso*Ergosterone (1·0 g.) in dry ether (50 c.c.) and methanol (5 c.c.) was added during 3 min. to a solution of lithium (0·5 g.) in liquid ammonia (200 c.c.). Stirring was continued for 35 min. and the ammonia allowed to evaporate overnight. The residue was diluted with water, and the product isolated with ether and crystallised from aqueous acetone, to give ergosta-4 : 22-dien-3-one (0·6 g.) as needles, m. p. and mixed m. p. 129—130°, $[\alpha]_D$ +41° (*c*, 0·9) (Found : C, 84·8; H, 11·2%). Light absorption : Max. at 2420 Å (ε 18,000).

5β-*Ergost*-22-*en*-3-*one*.—(*a*) *iso*Ergosterone (2·0 g.) in dry ethanol (50 c.c.) and a solution of potassium hydroxide (1·5 g.) in dry ethanol (30 c.c.) were shaken in hydrogen with freshly prepared 10% palladised charcoal (0·25 g.) in dry ethanol (10 c.c.). After 40 min., 2 mols. of hydrogen had been absorbed and the filtered mixture was worked up with ether, to give 5β-ergost-22-en-3-one in almost quantitative yield; this separates from ethanol as plates, m. p. 110°, $[\alpha]_D$ −5·2° (*c*, 2·1) (Found : C, 84·6; H, 11·8. Calc. for $C_{28}H_{46}O$: C, 84·35; H, 11·6%). Light absorption : Max. at 2070 (ε 1100) and 2700 Å (ε 107). 5β-Ergost-22-en-3-one gives a pale yellow colour with tetranitromethane in chloroform. Barton, Cox, and Holness (*loc. cit.*) give m. p. 110·5°, $[\alpha]_D$ −2°, −1°.

(*b*) Ergosta-4 : 22-dien-2-one (1·0 g.) was hydrogenated as described in (*a*) until absorption approximated to 1 mol. The product was 5β-ergost-22-en-3-one (0·45 g.) and it separated from ethanol as plates, m. p. and mixed m. p. 109—110°, $[\alpha]_D$ −5° (*c*, 2·0) (Found : C, 84·2; H, 11·7%). The 2 : 4-dinitrophenylhydrazone separates from benzene–ethanol as yellow needles, m. p. 197—198° (Found : N, 9·8. Calc. for $C_{34}H_{50}O_4N_4$: N, 9·7%).

3 : 3-*Dimethoxy*-5β-*ergost*-22-*ene*.—Crystallisation of 5β-ergost-22-en-3-one from methanol containing a trace of mineral acid gave 3 : 3-*dimethoxy*-5β-*ergost*-22-*ene* (72%) as blades, m. p. 84—85·5°, $[\alpha]_D$ −5·5° (*c*, 2·5) (Found : C, 81·4; H, 11·9; OMe, 14·7. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8; OMe, 14·0%). Light absorption : Max. at 2040 Å (ε 1900).

Hydrolysis. The dimethyl ketal (100 mg.) in dioxan (40 c.c.) was heated in aqueous sulphuric acid (0·5 c.c. of concentrated acid in 10 c.c. of water) under reflux for 1 hr. The product was isolated with ether and crystallised from ethanol, to give 5β-ergost-22-en-3-one (65 mg.) as plates, m. p. and mixed m. p. 109—111°, $[\alpha]_D$ −5·4° (*c*, 1·7).

5β-*Ergost*-22-*en*-3α-*yl Acetate*.—5β-Ergost-22-en-3-one (5·92 g.) in dry ether (100 c.c.) was added during 15 min. to a boiling solution of lithium aluminium hydride (6·0 g.) in dry ether (250 c.c.). After 1 hr., acetone (50 c.c.) was added, and the product isolated in the usual manner. Acetylation by warm acetic anhydride and pyridine followed by crystallisation from either ethanol or ethyl acetate–methanol gave 5β-ergost-22-en-3α-yl acetate (4·5 g.) as plates, m. p. 114—115°, $[\alpha]_D$ +9·2° (*c*, 1·3) (Found : C, 81·6; H, 11·7. Calc. for $C_{30}H_{50}O_2$: C, 81·4; H, 11·4%). Barton, Cox, and Holness (*loc. cit.*) give m. p. 114—115°, $[\alpha]_D$ +16°.

The acetate (136 mg.) was refluxed for ¾ hr. with methanolic potassium hydroxide (25 c.c.; 4%); isolation through ether gave 5β-ergost-22-en-3α-ol in quantitative yield; it separates from methanol as needles, m. p. 149—150°, $[\alpha]_D$ −6·2° (*c*, 1·6) (Found : C, 83·6; H, 12·3. Calc. for $C_{28}H_{48}O$: C, 83·9; H, 12·1%); Barton and Holness (*loc. cit.*) give m. p. 149—150°, $[\alpha]_D$ −4°. Reacetylation of the alcohol with acetic anhydride–pyridine at 80° gave 5β-ergost-22-en-3α-yl acetate, m. p. and mixed m. p. 114—115°, $[\alpha]_D$ +10° (*c*, 1·4).

3α-*Acetoxybisnorcholan*-22-*al*.—Ozonised oxygen was passed through a solution of 5β-ergost-22-en-3β-yl acetate (5·0 g.) in dry chloroform (150 c.c.) at −45° until a blue colour persisted. The solution was allowed to attain room temperature, glacial acetic acid (50 c.c.) and zinc dust (10 g.) were added, and the mixture was stirred for 2 hr. The filtered mixture was distilled in steam. After 1 l. of distillate had been collected, the non-volatile product was isolated by means of ether and crystallised from ethanol, to give the aldehyde (3·0 g.) as plates, m. p. 115—118°. Recrystallisation from ethanol or aqueous acetone gave 3α-*acetoxybisnorcholan*-22-*al* as plates, m. p. 121—123°, sintering at 115°, $[\alpha]_D$ +36° (*c*, 1·25) (Found : C, 77·1; H, 10·4. $C_{24}H_{38}O_3$ requires C, 77·0; H, 10·2%). The aldehyde does not show high-intensity light absorption above 2200 Å or give a colour with tetranitromethane in chloroform. The 2 : 4-*dinitrophenylhydrazone* of 3α-acetoxybisnorcholan-22-al, prepared in the usual manner, was purified by filtration of its benzene solution through a short column of Grade II alumina; it

separates from ethyl acetate as yellow needles, m. p. 205° (Found : N, 9·8. $C_{30}H_{42}O_6N_4$ requires N, 10·1%).

Extraction of the steam-distillate with chloroform gave an oil which on treatment with Brady's reagent yielded the 2 : 4-dinitrophenylhydrazone of 2 : 3-dimethylbutyraldehyde, separating from methanol as orange blades, m. p. 125 (lit., m. p. 124—125°).

3α-*Acetoxybisnorcholanic Acid*.—3α-Acetoxybisnorcholan-22-al (225 mg.) in glacial acetic acid (20 c.c.) was treated at 15° with a solution of chromium trioxide (50 mg.) in glacial acetic acid (10 c.c.) during 10 min. Next morning, methanol was added and the acidic product, which forms an insoluble sodium salt, was isolated in the usual manner. 3α-Acetoxybisnorcholanic acid (175 mg.) separates from acetone–light petroleum (b. p. 60—80°) as needles, m. p. 221—222°, $[\alpha]_D$ +21° (*c*, 1·4) (Found : C, 73·8; H, 9·8. Calc. for $C_{24}H_{38}O_4$: C, 73·8; H, 9·8%). Sawlewicz and Reichstein (*loc. cit.*) give m. p. 213—219° for this acid. The *methyl ester*, prepared by using ethereal diazomethane, separates from aqueous acetone as plates, m. p. 108—109°, $[\alpha]_D$ +29° (*c*, 2·8) (Found : C, 74·3; H, 10·2. $C_{25}H_{40}O_4$ requires C, 74·2; H, 10·0%).

20-*Oxopregnan*-3α-*yl Acetate*.—A mixture of 3α-acetoxybisnorcholan-22-al (m. p. 115—118°, 3·4 g.), freshly fused potassium acetate (1·75 g.), and acetic anhydride (25 c.c.) was kept at 135° for 6 hr., then poured into water containing some pyridine, and the product, isolated by use of ether as a brown gum, was dissolved in benzene–light petroleum (b. p. 60—80°) (200 c.c.; 1 : 9) and adsorbed on a column of Grade II alumina (50 g.). The column was washed with the same solvent mixture (400 c.c.), and the combined eluates were evaporated under reduced pressure, to give a colourless viscous oil (2·63 g.); in contrast to the parent aldehyde, the enol-acetate gives a yellow colour with tetranitromethane. The enol-acetate (2·6 g.) in chloroform (120 c.c.) was ozonised and the ozonide treated with zinc by the method described for the preparation of 3α-acetoxybisnorcholan-22-al, the steam-distillation being omitted. The product (2·1 g.), isolated by means of chloroform, was adsorbed from light petroleum (80 c.c.; b. p. 60—80°) on grade II alumina (20 × 2·5 cm.), and the column washed with light petroleum (160 c.c.; b. p. 60—80°) and benzene–light petroleum (b. p. 60—80°) (160 c.c.; 1 : 9). Evaporation of the combined eluates gave a gum (300 mg.) which was not examined. Further elution with benzene–light petroleum (b. p. 60—80°) (1·7 l.; 1 : 9 and 300 c.c.; 1 : 1) gave 20-oxopregnan-3α-yl acetate (1·2 g.) which separates from light petroleum (b. p. 60—80°) as thick rods, m. p. 100—101°, $[\alpha]_D$ +123° (*c*, 0·7) (Found : C, 76·8; H, 10·1. Calc. for $C_{23}H_{36}O_3$: C, 76·6; H, 10·1%). The keto-acetate was undepressed in m. p. when mixed with a specimen, m. p. 99—100°, $[\alpha]_D$ +121° (*c*, 1·0), prepared by reduction of pregnane-3 : 20-dione, followed by acetylation (Mancera, Ringold, Djerassi, Rosenkranz, and Sondheimer, *loc. cit.*).

3α : 20α-*Diacetoxypregnane*.—Continued elution of the alumina column described above, with benzene–methanol (200 c.c.; 1 : 1), gave an amorphous solid (280 mg.). This was acetylated (acetic anhydride and pyridine at 80°), and the product chromatographed in light petroleum (30 c.c.; b. p. 60—80°) on grade II alumina (10 × 1·0 cm.). Light petroleum (b. p. 60—80°) eluted a solid (170 mg.), crystallisation of which from light petroleum (b. p. 60—80°) gave 3α : 20α-diacetoxypregnane as needles, m. p. 180°, $[\alpha]_D$ +35° (*c*, 1·1) (Found : C, 74·0; H, 10·0. Calc. for $C_{25}H_{40}O_4$: C, 74·2; H, 10·0%). Hartman and Locher (*loc. cit.*) give m. p. 182—183°, $[\alpha]_D$ +35·3° (in C_6H_6).

3α-*Hydroxypregnan*-20-*one*.—20-Oxopregnan-3α-yl acetate (237 mg.) in methanol (20 c.c.) were heated with potassium carbonate (400 mg.) in water (5 c.c.) and methanol (10 c.c.) under reflux for 1 hr. Isolation by means of ether gave 3α-hydroxypregnan-20-one (214 mg.), needles [from acetone–light petroleum (b. p. 60—80°)], m. p. 147—148°, $[\alpha]_D$ +110° (*c*, 0·9) (Found : C, 79·2; H, 10·9. Calc. for $C_{21}H_{34}O_2$: C, 79·2; H, 10·8%). Meystre and Miescher (*loc. cit.*) gave m. p. 154°, $[\alpha]_D$ +110°. A mixture with a specimen prepared by the method of Mancera *et al.* (*loc. cit.*) {m. p. 145—147°, $[\alpha]_D$ +108° (*c*, 0·75)} was undepressed in m. p. Oxidation of 3α-hydroxypregnan-20-one with chromium trioxide gave pregnane-3 : 20-dione (85% yield), crystallising from light petroleum (b. p. 60—80°) as thick rods, m. p. 120—121° (lit., 123°), $[\alpha]_D$ +112° (*c*, 1·0) (Found : C, 79·5; H, 10·5. Calc. for $C_{21}H_{32}O_2$: C, 79·7; H, 10·2%).

We are glad to express our thanks to Glaxo Laboratories Ltd. for grants in aid of this work and for gifts of material; the receipt of a Maintenance award (to F. J.) from the Department of Scientific and Industrial Research is gratefully acknowledged.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, December 14th*, 1953.]

3 : 6-*Disubstituted Fluorenes. Part III.* Fluorene Analogues of Michler's Hydrol, Malachite-green, and Crystal-violet.*

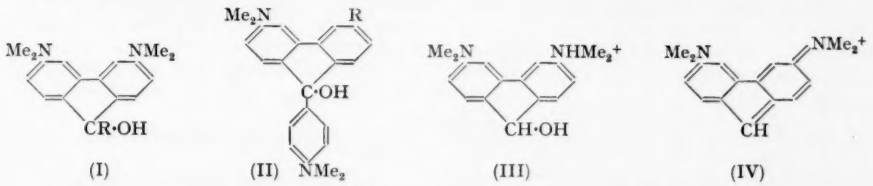
By A. Barker and C. C. Barker.

[Reprint Order No. 4900.]

The fluorene analogues of some basic di- and tri-phenylmethane dyes have been prepared and their absorption spectra determined. The analogues of malachite-green and crystal-violet show a very large bathochromic shift when compared with the corresponding triphenylmethane dyes; the analogue of Michler's hydrol blue is colourless and possesses the structure (III).

The results of *X*-ray analysis of fluorene have been interpreted by Iball (*Z. Krist.*, 1937, **34**, 397) in favour of a non-planar molecular configuration, and it seemed that further evidence about the problem might be obtained from the absorption spectra of fluorene analogues of basic triphenylmethane dyes. Accordingly, the analogues of Michler's hydrol (I; R = H), malachite-green base (I; R = Ph), and crystal-violet base (II; R = NMe_2) were prepared from 3 : 6-bisdimethylaminofluorenone. The unsymmetrical analogue of malachite-green base (II; R = H) was prepared from the colour salt obtained from 4′ : 4″-bisdimethylaminotriphenylmethane-2-diazonium sulphate, as described by Guyot and Granderye (*Bull. Soc. chim.*, 1905, **33**, 198).

The fluorenone was obtained by methylation of 3 : 6-diaminofluorene with trimethyl phosphate followed by oxidation with chloranil. It was identical with material obtained from 4 : 4′-bisdimethylaminobenzophenone-2-diazonium sulphate (Part II *); this confirms its structure. Attempts to methylate 3 : 6-diaminofluorenone with trimethyl phosphate or with methanol and hydrogen chloride were unsuccessful. Reduction of the methylated ketone with sodium amalgam gave 3 : 6-bisdimethylaminofluoren-9-ol (I; R = H) which is more reactive than the analogously constituted Michler's hydrol—recrystallisation caused deterioration, and boiling it with benzene and charcoal gave the parent ketone. It condensed normally with *NN*-dimethylaniline giving 3 : 6-bisdimethylamino-9-*p*-dimethylaminophenylfluorene.



3 : 6-Bisdimethylaminofluorenone and *p*-dimethylaminophenyl-lithium gave the analogue of crystal-violet base (II; R = NMe_2), the colour salt of which was identical with the dye obtained by Guyot and Haller (*Bull. Soc. chim.*, 1901, **25**, 750) by heating 4 : 4′ : 4″-trisdimethylaminotriphenylmethane-2-diazonium sulphate and oxidising the product. Similarly, the ketone and phenylmagnesium bromide gave the symmetrical analogue of malachite-green base (I; R = Ph). This base gave a yellow solution in acetic acid, thus disproving Dutt's claim (*J.*, 1926, 1171) to have prepared a green dye of this structure (cf. Part I, *J.*, 1953, 2034).

The Michler's hydrol analogue in glacial acetic acid showed no absorption band in the region 400—1000 mμ; instead, an ethanolic solution containing one equivalent of hydrogen chloride showed a band in the region 200—400 mμ which closely resembled that of 3 : 6-bisdimethylaminofluorene monohydrochloride (Fig. 1). The cation thus possesses the structure (III) and not the degenerate structure (IV). The absorption spectra of acetic acid solutions of the other dye bases are recorded in Fig. 2. They all show large batho-

* Part II, *J.*, 1954, 870.

chromic shifts when compared with their triphenylmethane analogues, and these shifts were tentatively ascribed to deviation from molecular planarity. Brown and Dewar (*J.*, 1954, in the press) have shown, however, that they can be quantitatively ascribed to the formation of the additional C–C bond. But the deviation from planarity deduced by Iball (*loc. cit.*) is not great, and, while these spectra provide no evidence in favour of non-planarity, they do not demonstrate that the dyes are completely planar.

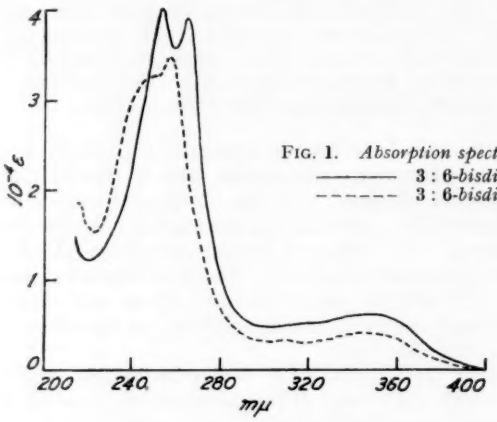


FIG. 1. *Absorption spectra of the hydrochlorides of :*
——— **3 : 6-***bisdimethylaminofluoren-9-ol, and*
– – – – – – **3 : 6-***bisdimethylaminofluorene in ethanol.*

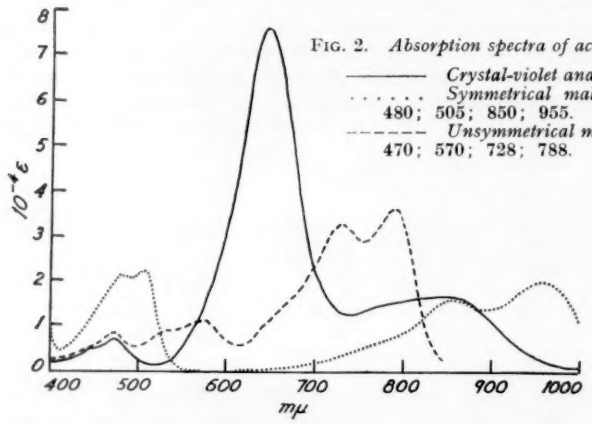


FIG. 2. *Absorption spectra of acetic acid solutions of :*
——— *Crystal-violet analogue.* $\lambda_{max.}$ (mμ) **470; 647; 850.**
. . . . . *Symmetrical malachite-green analogue.* $\lambda_{max.}$ (mμ) **480; 505; 850; 955.**
– – – – – – *Unsymmetrical malachite-green analogue.* $\lambda_{max.}$ (mμ) **470; 570; 728; 788.**

The blue solution of the crystal-violet analogue in acetic acid became progressively more violet upon dilution with water; Guyot and Haller (*loc. cit.*) observed a similar change when an ethanolic solution of the chloride of the dye was diluted. In water the chloride had $\lambda_{max.}$ **590 mμ**; $\varepsilon_{max.}$ $4{\cdot}22 \times 10^4$. This is probably due to polymerisation of the dye in water (cf. thionine; Rabinowitch and Epstein, *J. Amer. Chem. Soc.*, 1941, **63**, 69).

EXPERIMENTAL

3 : 6-*Bisdimethylaminofluorene.*—**3 : 6-**Diaminofluorene (9·0 g.; cf. Part II) and trimethyl phosphate (9·0 c.c.) were mixed and stirred at **160—170°** for **30** min. and at **190—200°** for **30** min., cooled, and then refluxed for **1** hr. with water (**130** c.c.) containing sodium hydroxide (22 g.). Water (200 c.c.) was added and the product was dried and refluxed for **30** min. with acetic anhydride (25 c.c.) which was then removed at **13** mm. The residue was sublimed at

140—150°/10^{-3} mm. and crystallised from ethanol (95 c.c.), giving **3 : 6-*bisdimethylaminofluorene*** (4·7 g.), m. p. 147—149° raised by chromatography on activated alumina in benzene–alcohol to m. p. 149° (Found : C, 81·0; H, 7·9; N, 10·9. $C_{17}H_{20}N_2$ requires C, 80·9; H, 8·0; N, 11·1%).

3 : 6-*Bisdimethylaminofluorenone*.—A mixture of chloranil (2·0 g.), **3 : 6**-dimethylaminofluorene (1·0 g.), and ethanol (40 c.c.) was refluxed for 75 min. and cooled, and the separated crystals were dissolved in hot dilute hydrochloric acid, and the solution was filtered and then made alkaline with sodium hydroxide. The dried precipitate was chromatographed in dry pyridine on activated alumina (1·5 × 5 cm.), and the eluate (75 c.c.) concentrated to 5 c.c. and slowly diluted with water (40 c.c.), giving orange crystals (0·70 g.), m. p. 250—252°; the m. p. of a mixture with material from 4 : 4′-bisdimethylaminobenzophenone-2-sulphate was 249—251° (Found : N, 10·2. Calc. for $C_{17}H_{18}ON_2$: N, 10·5%).

3 : 6-*Bisdimethylaminofluoren*-9-*ol*.—Sodium amalgam (3% of sodium; 3·5 g.), **3 : 6**-bisdimethylaminofluorenone (0·50 g.), and ethanol (95%; 30 c.c.) were stirred and refluxed for 1 hr. The solution was filtered and diluted with water, and the precipitate dried in vacuum, giving **3 : 6-*bisdimethylaminofluoren*-9-*ol*** (0·38 g.), m. p. 190—191° (Found : C, 76·4; H, 7·5; N, 10·5. $C_{17}H_{20}ON_2$ requires C, 76·1; H, 7·5; N, 10·4%).

3 : 6-*Bisdimethylamino*-9-*phenylfluoren*-9-*ol*.—**3 : 6**-Bisdimethylaminofluorenone (0·50 g.) was added to a refluxing solution of phenylmagnesium bromide, prepared from bromobenzene (1·1 c.c.) in ether (20 c.c.) and benzene (20 c.c.). A white solid separated; after being refluxed for 20 hr. the mixture was cooled and the white solid collected, stirred with aqueous ammonium chloride, and then dissolved in dilute hydrochloric acid. Basification of the filtered solution with ammonia solution and crystallisation of the product (0·24 g.) from benzene–light petroleum and then acetone, gave **3 : 6-*bisdimethylamino*-9-*phenylfluoren*-9-*ol***, m. p. 209—210° (decomp.) (Found : C, 79·6; H, 6·9; N, 7·9. $C_{23}H_{24}ON_2$ requires C, 80·2; H, 7·0; N, 8·1%). A further 0·24 g. was isolated from the reaction filtrate.

3 : 6-*Bisdimethylamino*-9-p-*dimethylaminophenylfluoren*-9-*ol*.—*p*-Dimethylaminophenyl-lithium was prepared from lithium (0·76 g.) and *p*-bromo-*NN*-dimethylaniline (10 g.) in ether (30 c.c.), and the solution filtered into a nitrogen-filled burette. A portion (2·3 c.c.) was added to a stirred mixture of benzene (50 c.c.) and **3 : 6**-bisdimethylaminofluorenone (0·40 g.) in an atmosphere of nitrogen. After 30 min. water was added, the benzene layer separated and dried (Na_2SO_4), the solvent removed, and the residue (0·41 g.) crystallised from ethanol, giving **3 : 6-*bisdimethylamino*-9-p-*dimethylaminophenylfluoren*-9-*ol*** as yellowish-white crystals, m. p. 196—198° (decomp.) (Found : C, 76·6; H, 7·3; N, 10·5. $C_{25}H_{29}ON_3$ requires C, 76·1; H, 7·5; N, 10·4%).

3-*Dimethylamino*-9-p-*dimethylaminophenylfluoren*-9-*ol*.—The ***colour salt*** corresponding to this base was prepared following Guyot and Granderye (*loc. cit.*), its warm aqueous solution basified with sodium hydroxide, the base extracted with benzene, and the solution dried (Na_2SO_4) and evaporated. The red residue solidified on trituration with light petroleum but did not crystallise (Found : N, 7·7. $C_{23}H_{24}ON_2$ requires N, 8·1%).

The authors gratefully thank Professor M. J. S. Dewar for his helpful interest in the work.

UNIVERSITY COLLEGE, HULL. [*Received, December 17th,* 1953.]

The Influence of Alkyl Groups upon Reaction Velocities in Solution. Part V. The Dissociation Constants of Ketone Cyanohydrins in Aqueous Alcohol.*

By D. P. Evans and J. R. Young.

[Reprint Order No. 4112.]

A study of the dissociation constants of the cyanohydrins of R·CO·R′ where R = C_6H_5, C_6H_{11}, or alkyl, and R′ varies through a series of alkyl groups for each R, indicates that the hyperconjugative electron release is an important factor in determining the stability of the ketone relative to the cyanohydrin. In *tert.*-butyl *iso*propyl ketone there is marked steric effect of the alkyl groups.

The hypothesis of hydrogen bonding in the transition complex during the acid-catalysed bromination of propiophenone was suggested in Part I (Evans, *J.*, 1936, 785) to explain the high activation energy of this reaction. Baker (*J.*, 1939, 1150) has interpreted the results of Part I on the basis of hyperconjugative electron release from methyl or methylene in alkyl phenyl ketones. It was stated in Part I (*loc. cit.*, p. 786) that, although yielding a possible interpretation of the changes in E_a, Baker and Nathan's (*J.*, 1935, 1844) postulates did not afford an explanation of the observed variations in the probability factor P of the kinetic equation $k = PZe^{-E_a/RT}$. Moreover, in the subsequent Parts of this series (*J.*, 1938, 1434; 1938, 1439; 1940, 339) evidence appeared in support of the hydrogen-bonding hypothesis. The many recent confirmations of the reality of hyperconjugation of alkyl groups, however, led us to attempt to decide which of the above explanations is the more correct. It was considered that the dissociation constants of ketone cyanohydrins might afford useful data towards this end and that, coupled with further work on the bromination of suitable dialkyl ketones (Part VI, following paper), a decision could be reached.

The work of Lapworth and Manske (*J.*, 1928, 2533; 1930, 1976) and of Baker and Hemming (*J.*, 1942, 191) had revealed that cyanohydrin equilibria are sensitive to structural and electronic influences, and moreover, this reaction may be used for unsymmetrical dialkyl ketones, which cannot be readily used in bromination experiments owing to the possibility of attack on either α-carbon atom (cf. Hey, Jones, *et al.*, *J.*, 1948, 272, 276).

The dissociation constants of a series of cyanohydrins (formed from the ketones R·CO·R′) determined by the method employed by Baker and Hemming (*loc. cit.*) in constant-boiling ethyl alcohol, triethylamine being used as catalyst at 35°, are given in Table 1. For convenience in discussing these results, series of compounds have been selected in each of which one group (R′) is constant while the other (R) varies from methyl through the alkyl series. The order of decreasing dissociation constants, *i.e.*, decreasing ketone stability, is the order of decreasing electron release towards the carbonyl group. Lapworth and Manske's results for the alkyl phenyl ketones are included for comparison; the values quoted have been calculated for 35° by multiplying their 20° values by 2·4. This factor was obtained by a subsidiary investigation of the temperature variation of the cyanohydrin dissociation constants of certain alkyl *cyclo*hexyl ketones and acetophenone which is reported in Table 1.

Table 1. *Cyanohydrin dissociation constants in constant-boiling ethyl alcohol at 20° and 35°.*

Ketone R·CO·R′					Ketone R·CO·R′				
R	R′	Temp.	100K	Error, %	R	R′	Temp.	100K	Error, %
Ph	Me	35°	333	3·0	*cyclo*Hexyl	Pr^n	20°	8·79	—
*cyclo*Hexyl	Me	20	3·51	1·7	*cyclo*Hexyl	Pr^i	20	8·69	—
*cyclo*Hexyl	Et	20	4·10	2·7					

Using Lapworth and Manske's results at 20° for acetophenone and the alkyl methyl ketones and the later results of this paper for the alkyl methyl and alkyl *cyclo*hexyl ketones

* Part IV, *J.*, 1940, 339.

at 35°, we obtain the values for the ratio K_{35}/K_{20} which are reported in Table 2. The constancy of K_{35}/K_{20} indicates the reasonable constancy of ΔH for each reaction. All the reactions involve the same kinds of bond rupture and formation, and an exact

TABLE 2. *Values of* K_{35}/K_{20} *for cyanohydrins of ketones* R·CO·R′.

Group R	Group R′					
	Me	Et	Pr^n	Pr^i	Bu^n	Bu^t
Ph	2·6	—	—	—	—	—
Me	2·3	2·0	2·5	3·5	2·6	2·4
*cyclo*Hexyl	2·2	2·4	2·4	2·5	—	—

constancy of ΔH is only prevented by minor variations of bond energies in the various structures and by small differences in the heats of solution. Hence the value 2·4, the mean of the Table 2 ratios, has been used for the conversion referred to above.

Alkyl phenyl ketones at 35°. Values for these dissociation constants are as follows :

R	n-C_6H_{13}	n-C_5H_{11}	Me	Bu^n	Pr^n	Et	Pr^i	Bu^t
100K	348	312	312	276	216	148	60	21

It is to be noted that there is inversion of the order of inductive electron release for the Me, Et, Pr^i, and Bu^t compounds, but the dissociation constants for the normal alkyl compounds increase steadily from ethyl to *n*-hexyl, and have regained the value for methyl phenyl ketone at the *n*-pentyl compound. The low value of K for the *tert.*-butyl compound indicates the absence of large steric effects of the type found by Hughes *et al.* (*J.*, **1946**, **157**, *et seq.*) in the *neo*pentyl halides, and since the values of $+I$ for the alkyl groups are not markedly different, it must follow that Baker's explanation that the variation of K is the result of hyperconjugation effects is correct. The conclusion that ***marked*** steric effects are absent does not preclude the possibility of proximity effects in this series of compounds.

In ascending the series of alkyl phenyl ketones from the ethyl ketone there is a progressive increase in the dissociation constant, which is maintained even up to the *n*-hexyl compound. We conclude that in this series there is a steric effect of the proximity type which increases with chain length and in which the long-chain structure is restricted in its movement by the larger volume occupied by the phenyl group. The results for the *cyclo*hexyl ketones, where a similar structural influence appears, support this view.

Alkyl methyl ketones at 35°. The following Table gives the values of these constants :

R	Pr^n	n-C_6H_{13}	n-C_5H_{11}	Bu^n	Bu^t	Me	Pr^i	Et
100K	9·11	8·95	8·50	8·27	7·61	7·03	5·42	5·33

In this series partial inversion occurs in the order of electron release from the last four groups, but the values of K for *n*-propyl and higher ketones are almost constant. As for the *n*-alkyl phenyl ketones, there is a minimum value of K at the ethyl member, but there is no ***marked*** fall in the dissociation constant in passing from acetone to ethyl methyl ketone. The approximate constancy of K for the *n*-propyl and higher members indicates the absence of proximity steric effect as found in the previous series.

Alkyl ethyl ketones at 35°. The relevant data are :

R	Bu^t	Bu^n	Pr^n	Pr^i	Me	Et
100K	17·5	10·3	9·96	6·19	5·33	4·94

The only inversions evident in this series are Me > Et and Pr^n > Pr^i. The picture is thus similar to that in the methyl series, except that *iso*propyl shows definitely greater electron release than ethyl.

Alkyl n-*propyl ketones at* 35°. The following values show that the four groups Bu^t, Pr^i, Et, and Me have attained the normal order of inductive electron release, the dissociation constant of di-*n*-propyl is still measurably greater than that of *n*-propyl *iso*propyl ketone, and there is no minimum value of K at the ethyl member.

R	Bu^t	Pr^n	Pr^i	Et	Me
100K	26·9	13·4	10·9	9·96	9·11

Alkyl iso*propyl ketones at* 35°. Here again the normal order of inductive release is found. However, the extremely high value of K for *tert.*-butyl *iso*propyl ketone indicates

R	Bu^t	Pr^i	Pr^n	Et	Me
$100K$	808	19·3	10·9	6·19	5·42

the appearance of a new steric factor in the reaction, the influence of which is also indicated in di*iso*propyl ketone by the appreciable difference between the *iso*- and the *n*-compound.

Alkyl cyclo*hexyl ketones at* 35°. In this series there are no inversions of position, and

R	Pr^n	Pr^i	Et	Me
$100K$	21·6	20·7	9·82	7·78

n- and *iso*-propyl are in better accord with the expected order of inductive electron release from these groups. As expected, this series is comparable with the alkyl *iso*propyl ketones and there is no minimum at the ethyl member.

Alkyl tert.-*butyl ketones at* 35°. In this series there is a qualitative repetition of the

R	Pr^i	Pr^n	Et	Me
$100K$	808	26·9	17·5	7·61

situation found in the *iso*propyl ketones. However, the appreciable increase in K for the ethyl over that for the methyl compound appears to indicate that some steric effect is present in the former, a conclusion which is supported by the further appreciable rise in K for the *n*-propyl and the very large increase observed for the *iso*propyl ketone.

Hyperconjugation Effects of Alkyl Groups in Ketones.—It is evident that in moving from the first to last of the above series of ketones, there is a change from a fully inverted sequence of the groups Me, Et, Pr^i, and Bu^t in the alkyl phenyl ketones to the normal sequence of inductive release when *iso*propyl, *cyclo*hexyl, or *tert.*-butyl is the constant group. The differences between the K values of the methyl and ethyl members of the various ketone series also show an interesting gradation :

Common group R...	Ph	Me	Et	Pr^n	Pr^i	*cyclo*Hexyl	Bu^t
$\Delta 100K_{(Me-Et)}$	164	1·7	0·39	−0·85	−0·77	−2·04	−9·89

$\Delta K_{(Me-Et)}$ is a measure of the difference between the sum of the effects of inductive and hyperconjugative electron release in the methyl and in the ethyl compounds, steric effects being absent, and the figures point to a marked influence of the phenyl nucleus on the hyperconjugative electron release from methyl in methyl phenyl ketone (cf. Baker *J.*, 1939, 1150). This influence of the other group attached to carbonyl is very small or absent in the dialkyl ketones.

Again the values of $\Delta K_{(Pr^n-Pr^i)}$ for the different series bring out a further interesting observation :

Common group R...	Ph	Me	Et	Pr^n	*cyclo*Hexyl	Pr^i	Bu^t
$\Delta 100K_{(Pr^n-Pr^i)}$	156	3·69	3·77	2·5	−0·9	−8·4	−780

The marked enhancement of hyperconjugation in the alkyl phenyl ketones is again shown here, but in addition there is indicated a very large effect in the opposite direction in the *tert.*-butyl ketones owing to a steric influence the exact nature of which is postulated below.

Steric Effects in Ketone Cyanohydrin Equilibria.—It is suggested that the steric impedance present in a given ketone is determined approximately by the extent and efficiency with which the approaches to carbonyl-carbon are screened, the side remote from the oxygen atom being particularly important. The absence of steric effects in methyl ketones establishes an arbitrary zero structure. Construction of molecular models and simple diagrams shows that in all ketones based on the groups Et, Pr^i, and Bu^t some restriction of alkyl-group rotation must occur and in the most highly branched ketone studied (*tert.*-butyl *iso*propyl ketone) rotation of either group is only possible if its motion is synchronised with that of the other. We thus attribute the large steric effect observed in the latter ketone to a steric meshing of the rotating groups.

The steric effect evident in the other structures (*e.g.*, phenyl and *cyclo*hexyl ketones

with normal alkyl groups having three or more carbon atoms in the chain) is regarded as being more random than the above and arises as the volume of rotation of the ring is increasingly entered by the irregular volume of the alkyl chain.

Experimental

Preparation of Ketones.—All ketones used, except a few purchased, were made by standard methods outlined below.

Alkyl methyl ketones were prepared by alkylation of acetoacetic ester with the appropriate alkyl halide or dialkyl sulphate. Acetone was used as a solvent, and a small amount of potassium iodide with twice the equivalent amount of potassium carbonate (based on the alkylating agent) were included in the reaction mixture which was stirred at reflux temperature until only traces of potassium carbonate remained. Finally, the reaction mixture was filtered, the solvent removed, and the derivative hydrolysed with excess of 2N-aqueous sodium hydroxide. Ethyl alcohol–ketone binary or ethyl alcohol–ketone–water ternary mixtures were obtained on distillation, and these were separated by repeated extraction with brine and distillation. Final yields were 40—50%.

Other alkyl ketones were made by reaction of aliphatic aldehydes with a suitable Grignard reagent; the alcohols were isolated and oxidised to the ketones by sulphuric acid–chromic acid in cold acetone (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39). The alkyl-*tert.*-butylcarbinols were made by a modification of Whitmore and Houk's general procedure (*J. Amer. Chem. Soc.*, 1932, **54**, 3714). The yields of carbinol were generally 60—70% except in the *cyclo*hexyl series for members above methyl, for which 40—50% yields were obtained, and for the *tert.*-butylcarbinols prepared from *tert.*-butyl chloride, for which approximately 20% yields were recorded. The oxidation of the alcohols was uncomplicated and the yields were usually 45—65%.

The final ketones showed physical constants (b. p.s and refractive indices) agreeing reasonably with those of Timmermans ("Physicochemical Constants of Pure Organic Compounds," Elsevier, 1950) or of Beilstein. Samples for equilibrium and kinetic study (see following paper) were obtained from the bulk yields above by stringent fractional distillation in which a small middle fraction, of boiling range $\geqslant 0{\cdot}3°$, was taken.

Equilibrium-constant Determination.—All measurements were made by a slight modification of Baker and Hemming's method (*J.*, 1942, 191). The solvent, constant-boiling ethyl alcohol, and the anhydrous hydrogen cyanide were similarly prepared; but all measurements at both 20° and 35° were made in sealed tubes and triethylamine instead of tri-*n*-propylamine was used as a catalyst. The ketones (*ca.* 0·3 mmole) were directly weighed into the drawn-out and calibrated tubes, which were stoppered during the operation. The walls were washed down with solvent, and 2 ml. of 1M-hydrocyanic acid in the solvent were added, followed by 1 ml. of 2% triethylamine solution also in the solvent. The volume was made up to approximately 9·8 ml. and finally adjusted to 10 ml. when the tube had been brought to the experimental temperature. The tube was then sealed.

All samples were kept for 24 hr. at 35° ± 0·05° or for 72 hr. at 20° ± 0·05° before analysis. The equilibrium concentration of hydrocyanic acid was determined by breaking the cleaned tubes by shaking in a wide-necked glass-stoppered bottle containing standard silver nitrate solution in slight excess over the expected hydrocyanic acid, in 75 ml. of 0·5% nitric acid. The contents were filtered and washed, the filtrate being made up to 150 ml. before titration with N/20-ammonium thiocyanate solution. In all experiments several blank determinations were performed, the titres so obtained serving as a measure of the amount of hydrocyanic acid added to the tests.

Specimen results for ethyl *cyclo*hexyl ketone are given below, the concentrations being expressed as equivalent ml. of N/10 per 10 ml. of solution. The general accuracy achieved was approximately ±3·0% which is comparable with that of Lapworth and Manske (*J.*, 1928, 2533). The unusually high dissociation of *tert.*-butyl *iso*propyl ketone led to very small consumption of

Cyanohydrin dissociation of ethyl cyclo*hexyl ketone at* 20°.

Time,		Initial volumes			Equilibrium volumes			
hr.	Ag^+	CNS^-	HCN	Ketone	HCN	Cyanohydrin	Ketone	$100K$
72	9·95	3·32	19·64	20·82	6·63	13·01	7·81	3·98
72	9·95	3·82	19·64	22·75	6·13	13·51	9·24	4·20
72	9·95	3·55	21·09	24·05	6·40	14·69	9·36	4·07
72	9·95	3·86	21·09	25·23	6·09	15·00	10·23	4·17

Mean value: $K \times 10^2 = 4{\cdot}10 \pm 0{\cdot}11$.

hydrocyanic acid, with the result that the accuracy here is considerably lower but the value is still sufficiently sound for the purposes of the discussion.

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The Influence of Alkyl Groups upon Reaction Velocities in Solution Part VI. The Acid-catalysed Prototropy of Dialkyl Ketones.*

By D. P. EVANS and J. R. YOUNG.

[Reprint Order No. 4113.]

The bromination of certain dialkyl ketones has provided results which, coupled with those of the previous papers, support Baker's views (*J.*, 1939, 1150) concerning the hyperconjugation of alkyl groups during prototropy as an explanation of changes in activation energy. Moreover, the changes of the PZ factor of the kinetic equation $k = PZ \cdot e^{-E_a/RT}$, may also be interpreted on the basis of hyperconjugation.

THE observations recorded in Part V * have shown that in the ketones R·CO·R′ conjugation in R affects the extent of hyperconjugative electron release from the alkyl groups R′. In order to apply these conclusions to the problem of the possible existence of hydrogen bonding in propiophenone and higher alkyl phenyl ketones (Parts I and II, *J.*, 1936, 785; 1938, 1434; cf. Baker, *J.*, 1939, 1150) the rates of acid-catalysed bromination of certain dialkyl ketones have been measured in 75% acetic acid. The results are given in the following Table, in which the values of k represent the fall in bromine titre in ml. of N/50-thiosulphate per min. for 20 ml. of 0·1M-ketone solution. Together with the results in Part I (*loc. cit.*), these results lead to the following conclusions.

Ketone	k_{15}	k_{25}	k_{35}	k_{45}	k_{55}	E (kcal.)	$\log_{10} PZ$
Me, Me	0·196	0·633	0·0272 (0°)	—	—	20·1	11·0
Et, Et	0·186	0·650	2·07	—	—	21·2	11·8
Pr^i, Pr^i	—	—	0·243	0·799	2·39	22·8	12·1
Pr^n, Pr^n	0·163	0·530	1·70	—	—	20·6	11·5
Bu^t, Me	—	0·281	0·889	2·42	—	20·3	10·9
Bu^t, Et	—	0·108	0·359	1·12	—	21·8	11·5
Bu^t, Pr^i * ...	—	—	0·0209	0·0718	0·207	22·7	11·1
Bu^t, Pr^n	—	0·096	0·308	0·096	—	21·3	11·1

* The results for this ketone are less satisfactory than the others (see p. 1316) but are sufficiently accurate for comparison.

Changes in Activation Energy.—(1) (*a*) The trends of the values of k and of E_a for the alkyl *tert.*-butyl ketones are similar to those found in Part I for the alkyl phenyl ketones. (*b*) The activation energy for *tert.*-butyl methyl ketone is only very slightly higher than that for acetone, which is identical with that for acetophenone. (*c*) The activation energy for *tert.*-butyl *iso*propyl ketone is measurably higher than any of the other values for the *tert.*-butyl series.

(2) In the dialkyl ketones, COR_2', the energy of activation for diethyl ketone is higher than that for acetone, and the value of E_a for di-*n*-propyl ketone approaches that of acetone. Finally, di*iso*propyl ketone exhibits a high E_a value equal to that of *tert.*-butyl *iso*propyl ketone.

Observation 1(*a*) is not unexpected owing to the similarity in the variable alkyl groups in both series, but in the light of the wide difference in values between the dissociation constants of the cyanohydrins of corresponding members for the phenyl and the *tert.*-butyl alkyl ketones, the similarity of the actual E_a values is surprising. We believe with Baker (*loc. cit.*) that the occurrence of a negative value of ΔE_a(Me − Et) in both the phenyl and the *tert.*-butyl series, together with the approximate equality of the activation energies for the methyl members and for acetone [observation 1(*b*)], results from a compensation of

* Part V, preceding paper.

hyperconjugation and inductive effects. This view also leads to a reasonable explanation of the changes in activation energies for the other dialkyl ketones.

Observation 1(*c*) is reminiscent of that found for the *iso*propyl group in combination with *tert.*-butyl in the cyanohydrin equilibria, where the very high dissociation constant of this ketone was explained on the basis of a steric (meshing) effect. A similar steric effect may operate in enolisation and hinder the approach of the proton to the ketone. With reference to observation 2, it is likely that a compensation of hyperconjugation and inductive electron release occurs which, coupled with steric effects in the branched-chain compounds, leads to the values of E_a observed.

Changes in the Factor log PZ.—The variations in log *PZ* for the dialkyl ketones are not large, but appear to be of sufficient magnitude and regularity to warrant interpretation on the basis suggested in Part I, *viz.*, that changes in *PZ* of the equation $k = PZe^{-E_a/RT}$ may be due to the electron accession to carbonyl carbon affecting the proportion of activated complexes which form enol. The significant values of $\log_{10} PZ$ from the present work and from Part I are listed below. In each case replacement of R′ = Me by Et raises

Ketone R·CO·R′			
R	R′	$\log_{10} PZ$	$\Delta \log_{10} PZ$
Ph	Me	10·7	
			+1·1
Ph	Et	11·8	
			−0·4
Ph	Pr^n	11·4	
			−0·7
Ph	Pr^i	11·1	
Me	Me	11·0	
			+0·8
Et	Et	11·8	
			−0·3
Pr^n	Pr^n	11·5	
			+0·3
Pr^i	Pr^i	12·1	

Ketone R·CO·R′			
R	R′	$\log_{10} PZ$	$\Delta \log_{10} PZ$
Bu^t	Me	10·9	
			+0·6
Bu^t	Et	11·5	
			−0·4
Bu^t	Pr^n	11·1	
			−0·4
Bu^t	Pr^i	11·1	

log *PZ*, the change being greatest in the phenyl compounds, less so in the methyl and ethyl compounds, and still less so in the *tert.*-butyl ketones. Further substitution of an additional methyl group to form the *n*-propyl ketones causes a fall in *PZ* in each case, and to a value intermediate between those for the corresponding methyl and ethyl compounds. Again, when the ethyl groups in the phenyl and *tert.*-butyl ethyl ketones are changed to *iso*propyl the values of *PZ* fall, but the value of *PZ* for the di*iso*propyl ketones is the highest of all the compounds studied. This similarity in trends and the regularity of the variations in *PZ* in these series support the view that the changes are real and justify an interpretation.

The increases in *PZ* on passing (*a*) from acetone to diethyl ketone and (*b*) from methyl to ethyl *tert.*-butyl ketone are comparable with the change observed by Evans (*J.*, 1936, 785) in changing from acetophenone to propiophenone. We are now of the opinion that the explanation put forward in Part I (*loc. cit.*) for the changes in *PZ* in the prototropy of the alkyl phenyl ketones is not correct, for it involves only the inductive effect of alkyl groups attached to the α-carbon atom.

Cardwell and Kilner (*J.*, 1951, 2431) reinvestigated and extended the earlier work of Catch, Elliott, Hey, and Jones (*J.*, 1948, 272) and Catch, Hey, Jones, and Wilson (*J.*, 1948, 276) on the ratio of the monobromination products of certain alkyl methyl ketones. They interpret the results on the basis of alkyl-group hyperconjugation with the developing double bond of the corresponding enol form. We are in full agreement with Cardwell and Kilner's conclusions on this point but wish to emphasize that the explanation provides strong corroborative evidence for the accuracy of the acid-catalysed enolisation mechanism proposed by Watson, Nathan, and Laurie (*J. Chem. Phys.*, 1935, **3**, 170), *viz.*,

$$R{\cdot}\underset{\underset{O}{\|}}{C}{\cdot}CH_2R' + H^+ \underset{2}{\overset{1}{\rightleftharpoons}} [R{\cdot}\overset{\delta+}{\underset{\delta-\,|}{C}}{\cdot}CH_2R'] \xrightarrow{3} R{\cdot}\underset{\underset{OH}{|}}{C}{=}CH{\cdot}R' + H^+$$
$$O(H^+)$$

in which the rate of bromination is influenced by the proportion of transition complexes which form enol (stage 3) rather than reverting to ketone.

The changes in *PZ* for the prototropy experiments can readily be interpreted on this principle. Thus it is observed that substitution of a hydrogen atom in the methyl group

of R·CO·Me by a methyl group introduces hyperconjugative electron release to the α-carbon atom during the formation of enol, with a consequent increase in the proportion of active complexes which form enol, and thereby enables us to account for the experimental increase in *PZ* for every R studied. The ionisation of the α-hydrogen atom, although probably affected by the inductive effect of α-methyl, is not influenced by the electromeric effects of the hyperconjugated hydrogen atoms, and in the formation of enol the hyperconjugation predominates over the inductive effect.

The case of di*iso*propyl ketone deserves special mention since here we have a symmetrical structure, and bromination in either group gives the same product. This, together with the hyperconjugation of six β-hydrogen atoms and the inductive effect of the α-methyl groups, gives a proportion of enol which is higher than in any of the other ketones studied.

The results and conclusions of this and the preceding paper clearly indicate that the hydrogen-bond hypothesis advanced in Part I of this series is incorrect.

Experimental

Materials.—The ketones were prepared as described in Part V (preceding paper).

Velocity Determinations.—The results for acetone quoted in the Table on p. 1314 were taken from Bonner, Evans, and Watson (*J.*, 1939, 1353).

The brominations were carried out in 75% acetic acid containing 0·5M-hydrochloric acid; the medium was prepared, and the experiments were conducted, in the manner described by Evans, Morgan, and Watson (*J.*, 1935, 1167) and by Evans (Part I, *loc. cit.*); a similar accuracy of ±1·5% was obtained in all cases but one. A typical set of results is given below.

Bromination of tert.*-butyl* n*-propyl ketone at* 35°.

Time (min.)	0	7	14	21	
Titre, ml. of N/50-$Na_2S_2O_3$ per 10 ml.	4·75	3·68	2·59	1·57	
Fall in titre per 10 ml.	—	1·07	2·16	3·18	
k_{35} (fall in titre per 20 ml. per min.)	—	0·306	0·309	0·303	Mean 0·306

With *tert.*-butyl *iso*propyl ketone there was a tendency for the value of k to fall during the course of the experiment. This was not prevented either by repurification of the ketone or by slight changes in technique. The variation was similar at all temperatures, and so the value of E_a for this ketone is less accurate than the others.

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The Influence of Alkyl Groups upon Reaction Velocities in Solution. Part VII. The Formation of Phenyltrialkylammonium Iodides in Methyl Alcohol.*

By David P. Evans.

[Reprint Order No. 4114.]

A study of the reactions between several dialkylanilines and methyl iodide has shown that in passing from alkylmethylanilines to diethyl-, ethylpropyl-, dipropyl-, or dibutyl-aniline there is a large increase in activation energy accompanied by a rise in the *PZ* factor of the kinetic equation. The observations have been interpreted as being due mainly to the steric effect of the alkyl groups higher than methyl.

The reaction between tertiary amines and alkyl halides, first studied by Menschutkin (*Z. physikal. Chem.*, 1890, **6**, 41; *Ber.*, 1895, **28**, 1399, and later papers) has since been further investigated by several workers. With the exception of those of Winkler and Hinshelwood (*J.*, 1935, 1147), Laidler (*J.*, 1938, 1786), Evans, Watson, and Williams (*J.*, 1939, 1345, 1348), and Brown and Fried (*J. Amer. Chem. Soc.*, 1943, **65**, 1841), the data are not suitable for analysis on the basis of the kinetic equation $k = PZ \cdot e^{-E_a/RT}$, which affords useful indications of the effects of the substituents upon reactivity. As an

* Part VI, preceding paper.

extension of the problem indicated in the title, the reaction between methyl iodide and several dialkylanilines has been studied at various temperatures in methyl alcohol as solvent.

Experimental

Materials.—The dialkylanilines were prepared by Hickinbottom's methods (*J.*, 1930, 992) and in all cases were freed from traces of primary and secondary bases by treatment with acetic anhydride and subsequent steam-distillation. The liquids boiled within 0·1° of the accepted temperature: Me_2, 95°/30 mm.; Et_2, 96°/13 mm.; Pr^n_2 122°/14 mm.; MeEt, 89·5°/15 mm.; $MePr^n$ 96·5°/10 mm.; $EtPr^n$, 111°/13 mm.

Measurements.—The reactions were carried out at three temperatures in absolute methyl alcohol in exactly the same manner as described by Evans, Watson, and Williams (*loc. cit.*). Satisfactory velocity constants were obtained by applying the simple bimolecular formula in the case of dimethyl-, ethylmethyl-, methylpropyl-, and dibutyl-anilines, but the other compounds showed slight autocatalysis. In these cases the slope of the tangent at zero time to the curve obtained on plotting $1/(a - x)$ against time gave constants which fell on the Arrhenius line. The tangents always passed through the first one or two points recorded, and extrapolation of the plot of k against percentage change also gave the same values of the velocity coefficients. A typical set of results is recorded below, where a = initial concentration of amine and iodide, x = concentration of the quaternary salt, and k is the velocity coefficient in l. mole^{-1} sec.$^{-1}$.

Ethylmethylaniline and methyl iodide at 65°.

a = 0·09754 mole/l.

Time (min.)	125	255	390	565	890	990	1140	1320
Titre (c.c. of 0·01131N-$AgNO_3$)	4·49	7·94	10·9	13·85	17·75	18·75	19·80	21·30
$k \times 10^4$	2·00	1·95	1·96	1·96	1·96	1·96	1·93	1·98

The following Table records the results for the velocity coefficients at various temperatures, together with the calculated values of the energies of activation and of log PZ.

NPhMe$_2$		NPhMeEt		NPhMePr^n	
Temp.	10^4k	Temp.	10^4k	Temp.	10^4k
25°	0·562	44·85°	1·97	44·8°	1·12
35·5	1·31	65	8·50	65·25	4·94
65	11·9	84·2	29·0	84·9	17·5
E = 15,200		E = 15,400		E = 15,430	
log PZ = 6·9		log PZ = 6·9		log PZ = 6·7	

NPhEt$_2$		NPhEtPr^n		NPhPr$^n_2$		NPhBu$^n_2$	
Temp.	10^4k	Temp.	10^4k	Temp.	10^4k	Temp.	10^4k
65°	1·24	65°	0·775	65·2°	0·548	85°	2·83
85·5	5·69	84·3	3·54	84·7	2·52	100	8·66
99·4	14·9	99·8	11·0	100	7·72	65	0·683
E = 18,000		E = 19,036		E = 19,060		E = 19,000	
log PZ = 7·7		log PZ = 8·2		log PZ = 8·1		log PZ = 8·1	

Discussion

The velocity constants at 65° decrease in the order

$$Me_2 > MeEt > MePr^n > Et_2 > EtPr^n > Pr^n_2 \simeq Bu^n_2;$$

indicating an approximately constant value for the di-*n*-propyl, the di-*n*-butyl, and presumably the higher di-*n*-alkyl compounds. The velocity coefficients at 65° referred to that of dimethylaniline as unity are given in the second line below:

Aniline	Me_2	MeEt	$MePr^n$	Et_2	Pr_2
k_{R_2}/k_{Me_2}	1·0	0·71	0·41	0·10	0·046
k_{R_2}/k_{Me_2}	1·0	0·66	0·44	0·07	—

and are in close accord with the same ratios (line 3) calculated from Thomas's results (*J.*, 1913, **103**, 594) for the reaction of these bases with allyl bromide at 40° in ethyl alcohol. The similarity appears to indicate that, although the absolute values of the coefficients in the two reactions differ by approximately 10^3, the variation in velocity from base to base is independent of the alkyl halide and is governed by the nature of the alkyl groups in the base.

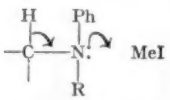
The formation of quaternary ammonium salts is facilitated by electron accession to the nitrogen atom (cf. Davies and Lewis, *J.*, **1934**, 1599; Evans, Watson, and Williams, *loc. cit.*), the increase in velocity due to an electron-repulsive *meta*- or *para*-nuclear substituent being caused entirely by the decrease in activation energy. Hinshelwood, Laidler, and Timm (*J.*, **1938**, 848) suggested that, since both the base strength and the energy of activation for quaternary salt formation appear to be governed by the reactivity of the unshared electron of the nitrogen, then for a given alkyl halide the activation energy should increase with decreasing strength of the tertiary base. They quoted several instances where the above rule was obeyed; *e.g.*, for the addition of methyl iodide to pyridine and triethylamine (in benzene) the activation energies are 14,300 and 9700 calories, respectively. In the dialkylanilines the slight increase in the inductive effect of the substituents as the alkyl series is ascended might be expected to cause a decrease in the activation energy; experiment, however, proves that this is not the case.

The results in the main Table show that, whenever the tertiary base contains two groups higher than methyl linked to nitrogen, the velocity coefficient is lower than that for the alkylmethylanilines.

A comparison of the energies of activation and the base strengths is instructive. The relevant data are given below, the values of pK_b being due to Hall and Sprinkle (*J. Amer. Chem. Soc.*, **1932**, **54**, 3469):

Alkyl groups	Me_2	MeEt	Et_2	MePr	EtPr	Pr_2
pK_b	5·06	5·98	6·56	5·64	6·34	5·57
E, cal.	15,200	15,400	18,000	15,430	19,030	19,060

Even in the base strengths the influence of the inductive effect of the alkyl groups does not offer a complete interpretation, since the ethyl substituent has a definite enhancing influence not present in methyl or *n*-propyl. On passing from dimethylaniline to the stronger bases diethyl-, dipropyl-, or ethylpropyl-aniline the activation energies for the addition of methyl iodide *increase* by a considerable amount (3000 cal., approx.) instead of decreasing as expected on Hinshelwood, Laidler, and Timm's suggestion, whilst for the alkylmethylanilines which vary appreciably in strength, the activation energies are approximately constant. Baker (*Trans. Faraday Soc.*, **1941**, **37**, 647) suggested that the increase in activation energy in the diethyl- and higher dialkyl-anilines may be due to the decreased electron release according to the mechanism inset. Since the alkyl group is so close to the seat of the reaction, such an effect might have a large influence on the activation energy. Moreover, the alkyl groups are linked through nitrogen to the conjugate phenyl nucleus, which enhances the hyperconjugation of methyl. This large hyperconjugate electron release operates most strongly in dimethylaniline, and is reduced in ethylmethylaniline, as indicated by change in pK_b. Brown and Fried's observation (*loc. cit.*) that steric hindrance occurred in the reaction of methyl iodide with



$C_6H_4\cdot[CH_2]_n\cdot NMe$ when n changed from 3 to 4, with a sudden rise in activation energy of approximately 5000 cal., is similar to some of the present results where large increases in E occur between successive members of homologous series, *viz.*,

$$Me,Et\text{–}Et_2,\ \Delta E = 2600 \text{ cal.};\quad Me,Pr\text{–}Et,Pr,\ \Delta E = 3600 \text{ cal.}$$

Moreover, the smaller difference in E values between diethyl- and ethyl-*n*-propyl- (1030 cal.), and the negligible difference between ethyl-*n*-propyl- and di-*n*-propyl-aniline, seems to point to a "saturation" value being reached. In the diethyl- and higher dialkyl-anilines, therefore, it is likely that steric effects of the type described by Brown and Fried (*loc. cit.*) come into play in addition to electronic influences and it is difficult to separate the effects.

I thank Dr. R. Williams for experimental assistance.

Glamorgan Technical College, Treforest. [*Received, February 19th,* **1953**.]

*Aluminium Halide Complexes with Pyridine, Trimethylamine, and Triethylamine. Part II.**

By D. D. Eley and H. Watts.

[Reprint Order No. 4880.]

Heats of solution have been measured, and dissociation energies calculated, for seven crystalline 1 : 1 complexes, C_5H_5N,AlX_3 and Me_3N,AlX_3 (where X = Cl, Br, or I) and $Et_3N,AlCl_3$. The heat of solution found for AlI_3 (c) of 135 ± 0·8 kcal. is much greater than the previously accepted value of 89. The dissociation energies are used in a discussion of heats of mixing of donor and halide molecules, and to decide whether there is only one ligand. The dissociation energies observed are larger for these AlI_3 complexes than for those with $AlBr_3$ and $AlCl_3$, and this is attributed to a relatively small reorganisation energy of the AlI_3 radical, the actual N→Al bond-dissociation energy being approximately constant in all cases. Values for the aluminium–halogen bond energies are calculated and discussed.

This paper describes the results of a determination of dissociation energies for the seven crystalline 1 : 1 complexes involving the N→Al link described in Part I.* Heats of solution of a given complex, and its component donor and acceptor molecules, have been determined in 2N-hydrochloric acid.

$$R{\rightarrow}AlX_3\ (c) \longrightarrow R\ (2N\text{-}HCl) + AlX_3\ (2N\text{-}HCl) \quad . \quad . \quad . \quad . \quad Q_S(1)$$

$$R\ (l \text{ or } g) \longrightarrow R\ (2N\text{-}HCl) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad Q_S(2)$$

$$AlX_3\ (c) \longrightarrow AlX_3\ (2N\text{-}HCl) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad Q_S(3)$$

Then, for the dissociation in the condensed phase,

$$R{\rightarrow}AlX_3\ (c) \longrightarrow R\ (l \text{ or } g) + AlX_3\ (c) \quad . \quad . \quad . \quad . \quad . \quad . \quad -D_c$$

we define a dissociation energy D_c (heat, $-D_c$), which is therefore given by

$$D_c = Q_S(2) + Q_S(3) - Q_S(1)$$

Experimental

The complexes were available in sealed, evacuated, glass bulbs, each holding about 0·1 g. The calorimeter used was the thermistor calorimeter described by Dilke, Eley, and Sheppard (*Trans. Faraday Soc.*, 1950, **46**, 261), with a bulb-breaking attachment fitted in place of the liquid delivery tube. Each experiment consisted in breaking a bulb of complex under 100 ml. of 2N-hydrochloric acid, and was followed by electrical calibration by passage of a known current through a coil of "Bright-ray" wire of resistance 20·32 Ω. All measurements were at 25°.

Before examination of the complexes, the calorimeter was checked by a determination of the heat of neutralisation. Four experiments were made in which accurately known amounts (0·5—1 ml.) of 5N-hydrochloric acid, contained in bulbs, were broken under 100 ml. of 0·05N-sodium hydroxide. The heat of neutralisation calculated by the least squares method was 14·6 kcal./mole, with a probable error of 0·2 kcal. Richards and Rowe (*J. Amer. Chem. Soc.*, 1920, **42**, 1621; 1921, **43**, 770; 1922, **44**, 684) give, for 20°,

$$HCl,400H_2O + NaOH,400H_2O = NaCl,801H_2O \quad Q_M = 13{\cdot}761 \text{ kcal.}$$

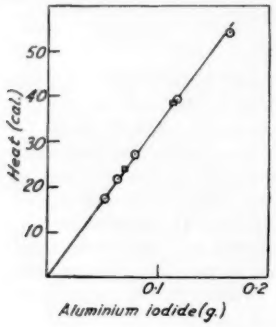
To this we add a heat of dilution of 1·2 kcal./mole for the hydrochloric acid, those for sodium hydroxide and sodium chloride being negligible, and subtract 0·275 kcal. for the temperature effect on the heat of reaction. The result is then 14·7 kcal./mole, in agreement with our observed values. The estimated accuracy of the measurements is 1%.

Results

Usually five determinations were made with each substance, with different weights, and 100 ml. of 2N-hydrochloric acid. The results were plotted as heat evolved against weight of substance, and the best straight line was drawn by the method of least squares. The slope gave the heat of solution per gram of substance, which was converted into the heat of solution per mole (for the aluminium halides, the molecular weight of the monomer AlX_3 was used here).

* Part I, *J.*, 1952, 1914.

The results are given in Table 1, values for the individual experiments being listed in the thesis of H. Watts (Bristol, 1952). An example of the procedure, for the case of aluminium iodide, is shown in the Figure.



The heat of solution of aluminium iodide in water (squares) and in 2N-hydrochloric acid (circles).

TABLE 1. *Heats of solution, Q_S, and dissociation energies (condensed phase), D_C, at 25°.*

Substance	No. of expts.	Q_S (kcal./mole)	D_C (kcal./mole)	Substance	No. of expts.	Q_S (kcal./mole)	D_C (kcal./mole)
$AlCl_3$ (c)	6	77·5 ± 0·6	—	AlI_3 (c)	7 *	135 ± 0·8	—
$C_5H_5N,AlCl_3$ (c)	6	54·5 ± 0·8	31·8	C_5H_5N,AlI_3 (c)	4	68·7 ± 1·2	75·1
$Me_3N,AlCl_3$ (c)...	5	63·6 ± 0·9	30·8	Me_3N,AlI_3 (c)	4	75·2 ± 1·6	76·7
$Et_3N,AlCl_3$ (c)	5	69·3 ± 1·7	28·5				
				C_5H_5N (l)	3	8·8 ± 0·2	—
$AlBr_3$ (c)	5	86·5 ± 0·5	—	Me_3N (l)	6	16·9 ± 0·2	—
$C_5H_5N,AlBr_3$ (c)	5	63·4 ± 0·7	31·9	Et_3N (l)	5	20·3 ± 0·7	—
$Me_3N,AlBr_3$ (c)	5	70·4 ± 1·0	33·0				

* Two of these experiments were with water as solvent and agreed with those with 2N-HCl (cf. Figure).

DISCUSSION

First we compare our values of Q_S with those available in the literature.

The Aluminium Halides.—The heats of solution obtained by us agree closely with earlier values in the cases of aluminium chloride and bromide, but there is a large discrepancy in the case of the iodide. Thus, for aluminium chloride, Bichowsky and Rossini ("Thermochemistry of the Chemical Substances," Reinhold Publishing Corp., New York, 1936) list four values of the heat of solution in water, averaging 77·2 ± 0·9 kcal./mole, and, in addition, there are values of 78·09 (H_2O) and 78·59 (0·02N-HCl) (Roth and Buchner, *Z. Elektrochem.*, 1934, **40**, 87), 71·7 ± 0·1 (0°; 20% HCl) (Klemm and Tanke, *Z. anorg. Chem.*, 1931, **200**, 343), and 79·4 kcal. (H_2O) (Roth and Börger, *Z. Elektrochem.*, 1938, **44**, 540). For aluminium bromide, Bichowsky and Rossini give values of 85·3 and 90·0, and Klemm and Tanke 89·9 (0°; 20% HCl). There appear to be only two values available for aluminium iodide, 89·0 (9°; H_2O) (Berthelot, see Landolt–Börnstein, "Tabellen," Vol. II, p. 1554) and 89·9 (0°; 20% HCl) (Klemm and Tanke, *loc. cit.*). These values are very much smaller than the 135 kcal./mole found in this work, and the difference is much too large to arise from differences in the conditions of experiment, such as temperature or acid concentration. Two probable causes for the earlier values are impurities in the aluminium iodide used, and incomplete dissolution. The only cause for too high a value for the heat of solution would be an error in the electrical calibration of the calorimeter. This is ruled out, first by the good reproducibility of the experiments with aluminium iodide, and secondly by checks on the calorimeter before and after the aluminium iodide runs. The checks "before" consist not only in the heats of neutralisation, but also in the heats of solution of the chloride and bromide. The check "after" consists in the value for the heat of solution of trimethylamine of 16·9 kcal. This corresponds to the reaction

$$Me_3N(l) + H^+(aq) + Cl^-(aq) \longrightarrow Me_3NH^+(aq) + Cl^-(aq)$$

The following data are available :

$$Me_3N(l) + aq \longrightarrow Me_3N(aq),\ Q_s = 8{\cdot}75 \text{ kcal.}$$
$$Me_3N(aq) + H^+(aq) + X^-(aq) \longrightarrow Me_3NH^+(aq) + X^-(aq),\ 8{\cdot}828 \text{ kcal.}$$

The first figure is from the International Critical Tables (Vol. V, p. 149), and the second from Everett and Wynne-Jones (*Trans. Faraday Soc.*, 1939, **35**, 1380). The sum of these gives 17·58 kcal., which agrees with our value, within uncertainties arising from heats of dilution, differences in anions, etc.

Taking our heats of solution, and the other necessary data from Bichowsky and Rossini (*op. cit.*), we obtain the following values for the heats of formation of the aluminium halides at 25° from the elements in their standard states (figures given by Bichowsky and Rossini are in parentheses) :

$$Q_f\ [AlCl_3\ (c)] = 167{\cdot}9 \text{ kcal./mole } (166{\cdot}8)$$
$$Q_f\ [AlBr_3\ (c)] = 125{\cdot}8 \text{ kcal./mole } (126{\cdot}7)$$
$$Q_f\ [AlI_3\ (c)] = 31{\cdot}4 \text{ kcal./mole } (77{\cdot}2)$$

Heats of Mixing.—A considerable number of measurements of heats of mixing of donor with aluminium halide in the presence of chlorobenzene as diluent have been made in this laboratory (Dilke, Eley, and Sheppard, *Trans. Faraday Soc.*, 1950, **46**, 261; D. J. A. Dear, Thesis, Bristol, 1951). These correspond to the reaction

$$AlX_3 \text{ (under PhCl)} + nR\ (l) \longrightarrow R_n,AlX_3\ (c, \text{ or s in PhCl}) + Q_M$$

While there is some uncertainty in the initial and the final state, *i.e.*, whether crystalline or in solution, the main uncertainty which affects interpretation of Q_M lies in the value of n, excess of the donor R being used. We may now compare values of Q_M with values of D_C in certain cases and thus throw light on the value of n. We have

$C_5H_5N,AlCl_3$	$Q_M = 47{\cdot}8$ (Dilke *et al.*)	
corrected to	$Q_M = 42{\cdot}6$ (Dear, *loc. cit.*)	$D_C = 31{\cdot}8$
$Et_3N,AlCl_3$	$Q_M = 24{\cdot}0$ (Dilke *et al.*)	$D_C = 28{\cdot}5$
$C_5H_5N,AlBr_3$	$Q_M = 60{\cdot}1$ (Dear)	$D_C = 31{\cdot}9$
C_5H_5N,AlI_3	$Q_M = 70{\cdot}1$ (Dear)	$D_C = 75{\cdot}1$

The agreement is reasonable enough in cases two and four to allow us to conclude that here n, the number of ligand molecules, is restricted to unity. In the first case, the discrepancy indicates that further molecules of donor are taken up beyond $n = 1$, probably by weak dipole forces. In support of this view we have found it possible to prepare a crystalline complex, of m. p. 15°, by addition of excess of pyridine to aluminium chloride in the presence of benzene. The analysis and molecular weight of this complex corresponded to $3C_5H_5N,AlCl_3,3C_6H_6$, and it was possible to remove considerable amounts of first benzene, then pyridine, by pumping *in vacuo*.

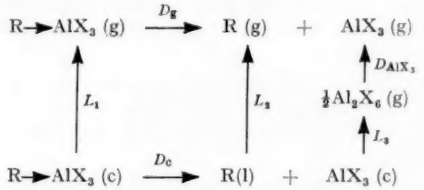
Fisher–Hirschfelder models show that the bulky triethylamine molecule effectively screens the aluminium atom from accepting more than one donor molecule, while the flat pyridine molecule, if held by the nitrogen atom, should permit further pyridine molecules to approach the aluminium atom to be held by dipole forces. This probably explains the difference between $Et_3N,AlCl_3$ ($n = 1$) and $(C_5H_5N)_n,AlCl_3$ ($n > 1$). With C_5H_5N,AlI_3, the iodine atoms, being much larger than bromine or chlorine, will tend to restrict additional donor molecules from approaching the aluminium, although by itself this effect is probably too small to be decisive. In addition, we expect a smaller positive charge on the aluminium atom for the bromide and iodide than for the chloride. From electronegativities it is possible to estimate bond moments for AlCl 4·0 D, AlBr 3·2 D, and AlI 1·4 D; and we should, therefore, expect the tendency for dipolar addition to fall in this order, as observed. Higher complexes, such as $3C_5H_5N,AlBr_3$ reported by Müller (*Z. anorg. Chem.*, 1926, **156**, 65) and Jacober and Kraus (*J. Amer. Chem. Soc.*, 1949, **71**, 2705) support this suggestion for aluminium bromide.

The N→Al *Bond Dissociation Energy. Dissociation of the Solid Complex into Gaseous Components.*—It is possible to analyse the dissociation energy in the condensed phase, D_c, so as to obtain D(N→Al), the dissociation energy of the N→Al bond, on the basis of certain

reasonable assumptions. Consider D_g, the dissociation energy of the complex in the gas phase into donor and monomer aluminium halide, given by

$$D_g = L_2 + D_{AlX_3} + L_3 + D_c - L_1$$

where the energy terms are defined by the cycle below



To obtain D_g from D_c requires a knowledge of L_1, the latent heat of sublimation of the complex, which is not available for our complexes. Klemm, Clausen, and Jacobi (*Z. anorg. Chem.*, 1931, **200**, 363) found the following values of L_1 for the ammonia complexes: NH_3,$AlCl_3$ 20 kcal./mole; NH_3,$AlBr_3$ 21 kcal./mole; NH_3,AlI_3 22 kcal./mole. This suggests that L_1 varies very little from chloride to bromide, so that we may usefully discuss the quantity $D_g + L_1$, which is the dissociation energy of the crystalline complex into gaseous components, D_{cg}, *viz.*:

$$R{\rightarrow}AlX_3\ (c) \longrightarrow R\ (g) + AlX_3\ (g),\ D_{cg} = D_g + L_1$$

Values of D_{cg} for the comp exes are listed in the first part of Table 2. Values of L_3 used are: $AlCl_3$ 13·5, $AlBr_3$ 9·7, and AlI_3 12·1 kcal., and those of D_{AlX_3} are: $AlCl_3$ 14·5, $AlBr_3$ 13·3, and AlI_3 11·3 kcal. (Fischer and Rahlfs, *ibid.*, 1932, **205**, 1). Values used for L_2 are 8·5 kcal./mole for pyridine (Mathews, *J. Amer. Chem. Soc.*, 1926, **48**, 562), 5·7 for trimethylamine (Swift and Hochandel, *ibid.*, 1945, **67**, 880), and 7·9 for triethylamine (Thompson and Linnett, *Trans. Faraday Soc.*, 1936, **32**, 681).

The N→Al *Bond Dissociation Energy.*—(a) *Variation with donor.* Reference to the D_{cg} values in the first part of Table 2 shows a small decrease over the series $C_5H_5N > Me_3N$, $Et_3N > NH_3$. The work of H. C. Brown and his colleagues has established the following D_g values for the dissociation of gaseous trimethylboron complexes: Me_3N 17·62, pyridine 17, NH_3 13·75, and Et_3N probably <10 kcal. (*J. Amer. Chem. Soc.*, 1944, **66**, 435; 1947, **69**, 1137, 1332). Our results show a relatively high value for pyridine for D_{cg} ($= D_g + L_1$) which may be a result of a somewhat higher value for the latent heat of sublimation L_1, although this is not by any means certain, as the pyridine complexes had the lowest melting point (cf. Part I) of those examined. The main difference concerns the triethylamine complex, and we are led to postulate that the steric forces which Brown and Taylor (*loc. cit.*, p. 1332) show to be responsible for the low heat with trimethylboron, are much smaller with aluminium chloride. This is what one would expect, as the B–C bond is only 1·56 Å in trimethylboron (Levy and Brockway, *ibid.*, 1937, **59**, 2085) compared with Al–Cl 2·06 Å (Palmer and Elliot, *ibid.*, 1938, **60**, 1852), so that there will be more crowding of groups attached to the donor and acceptor atoms.

(b) *Variation over series chloride to iodide.* For a discussion of this variation it would be desirable to know D_g, the dissociation energy of the gaseous complex. We may consider this process to occur in two stages, with the energy steps

$$R{\rightarrow}AlX_3\ (g) \xrightarrow{D(N{\rightarrow}Al)} R\ (g) + AlX_3\ (g,\ tetrahedral) \xrightarrow{-K} AlX_3\ (g,\ planar)$$

and to involve a dissociation energy of the N→Al bond followed by a reorganisation energy K of the AlX_3 radical, so

$$D_g = D(N{\rightarrow}Al) - K$$

The reorganisation energy K was introduced for boron fluoride–ether complex by Bauer, Finlay, and Laubengayer (*J. Amer. Chem. Soc.*, 1943, **65**, 889). For the aluminium halides we may estimate K by a method given in the Appendix, and it is found to decrease

strongly over the series chloride to iodide: $AlCl_3$, 79·5, $AlBr_3$ 65·7, AlI_3 35·7 kcal. This behaviour may account very largely for the observed values of D_{cg}. Thus

$$D(N\rightarrow Al) = D_g + K$$
$$D(N\rightarrow Al) + L_1 = D_g + L_1 + K = D_{cg} + K$$

and we obtain the results shown in the second part of Table 2. It is clear that while D_{cg} varies greatly over the series chloride to iodide, the quantity $[D(N\rightarrow Al) + L_1]$ remains nearly constant. Taking the values for the ammonia complexes, and using

TABLE 2. *Dissociation energy of complexes.*

	D_{cg} (kcal.) [1]			$D(N\rightarrow Al) + L_1$ [2] (kcal.)		
Ligand	$AlCl_3$	$AlBr_3$	AlI_3	$AlCl_3$	$AlBr_3$	AlI_3
C_5H_5N	68·3	63·4	107·0	148	129	143
Me_3N	64·5	61·7	105·8	144	127	141
Et_3N	64·4	—	—	144	—	—
NH_3	60·0	62·0	100·0	139	128	136

[1] $D_{cg} = D_g + L_1$, *i.e.*, solid complex ⟶ gaseous components. [2] $D(N\rightarrow Al) + L_1 = D_{cg} + K = D_g + L_1 + K$. [3] Klemm, Clausen, and Jacobi (*loc. cit.*) give the following D_e values; NH_3,$AlCl_3$ 32; NH_3,$AlBr_3$, 39; NH_3,AlI_3 32. We accept the first two, but change the last to 77, as a result of taking the heat of solution of AlI_3 (c) as 135 instead of 78·9. The D_{cg} values are calculated from these D_e values for comparison with our own data, although Klemm *et al.* obtained L_1 and hence D_g values, which are more fundamental than D_{cg}.

the L_1 already given, we obtain $D(N\rightarrow Al)$ values of 118, 107, and 114 kcal. for the chloride, bromide, and iodide respectively, *i.e.*, an average value of 113 kcal. for the three halides. The $[D(N\rightarrow Al) + L_1]$ values for the other bases are higher than for the ammonia complexes, but the L_1 values would also be expected to be higher, and to vary little over the halide series. Therefore it seems reasonable to suggest the following two conclusions: $D(N\rightarrow Al)$ is (*a*) nearly constant over all the complexes examined, and (*b*) approximately 113 kcal. Conclusion (*b*) is more speculative than conclusion (*a*), and since the K values used in the calculations are upper values (cf. Appendix 2), the figure 113 will also be an upper value. However, it scarcely seems likely that $D(N\rightarrow Al)$ will fall below 90 kcal. and the result that $D(N\rightarrow Al)$ lies in the range 90—113 kcal. remains of great interest. An interesting future problem is now to see whether such a magnitude can be justified on theoretical grounds.

APPENDIX

1. *Bond Energy of Aluminium–Halogen Bonds.*—We write $E(Al–X)$, the bond energy of Al–X, as $\frac{1}{3}Q_{fg}$, where Q_{fg} is the heat of formation of AlX_3 monomer from Al and X atoms in the gas phase:

$$Q_{fg} = Q_f + 55 + \tfrac{3}{2}L_4 - D_{AlX_3} - L_3$$

where Q_f, D_{AlX_3}, and L_3 are defined (values given earlier in this paper), 55 kcal. is the heat of sublimation of aluminium, and L_4 is the energy change of the process X_2 (c, l, or g) ⟶ 2X(g), taken from Bichowsky and Rossini (*op. cit.*).

As a matter of interest, we also consider AlF_3, taking $Q_f = 311$ kcal. (quoted by Irmann, *Helv. Chim. Acta*, 1950, **33**, 1449), $L_3 = 59$ kcal., and, since double molecules are not formed, $D_{AlF_3} = 0$ and $L_4 = 63·5$ kcal. (Naryshkin, *Chem. Abs.*, 1940, **34**, 1237). Bond energies so calculated are listed as $E(Al–X)$ obs. in Table 3.

TABLE 3. *Bond energies, kcal./mole.*

Bond	Al–F	Al–Cl	Al–Br	Al–I
$E(Al–X)$ obs.	134	94	79	47
$E(Al–X)$ calc.	194	99	80	55

We have also calculated values of $E(Al–X)$ by using Pauling's equation, together with his values for single-bond energies and electronegativities ("Nature of the Chemical Bond," Cornell University Press, New York, 1939, p. 60) and with the assumption that $E(Al–Al) = \frac{2}{3}S$, where S is the sublimation energy, which assumes that in the sublimation we have to break 3 covalent bonds each involving 2 atoms. Pauling has apparently based his electronegativity value for Al on this assumption (*op. cit.*, p. 63), applied to an unstated compound or compounds of aluminium. (We are essentially dealing with an empirical procedure.) The results in

Table 3 seem to justify the method *a posteriori*, except for the case of Al–F. It seems likely that Pauling's electronegativity value of 4·0 for fluorine is too high; a lower value would also be consonant with the suggestion of Evans, Warhurst, and Whittle (*J.*, 1950, 1524), that the electron affinity of the element is less than that of chlorine.

2. *Estimate of Reorganisation Energy, K.*—Consider the energy of the process, $Al_2X_6 \longrightarrow 2AlX_3$, $2D_{AlX_3}$. The initial process is the rupture of two Al–X *bridge* bonds $(Al–X)_b$, followed by the change tetrahedral to planar in the AlX_3 radicals, therefore

$$2D_{AlX_3} = 2D(Al–X)_b - 2K$$

We now *assume* that $D(Al–X)_b$ may be aproximated by $E(Al–X)$ given in Table 3, *i.e.*, we equate the energy of the Al–X bridge bond to that of the normal bond. Palmer and Elliott (*loc. cit.*) show the former to be longer than the latter, the differences in length being 0·15 Å for the chloride, 0·12 Å for the bromide, and 0·05 Å for the iodide. Thus the bridge bonds are probably very little weaker than the normal bonds, for example, in the extreme case of Al–Cl by only 2·6 kcal. The force constant of the Al–Cl bond is $1·6 \times 10^5$ dynes/cm. (Kohlrausch and Wagner, *Z. physikal. Chem.*, 1942, **52**, 185), so the energy required to stretch it by 0·15 Å is only this amount. With this assumption and using the known D_{AlX_3} values (Fischer and Rahlfs, *loc. cit.*), we calculate

$$K(AlCl_3) = 79·5;\ K(AlBr_3) = 65·7;\ K(AlI_3) = 35·7 \text{ kcal.}$$

Because of the above assumptions, these values will be upper limits for the reorganisation energies, but should faithfully reflect the differences between the chloride, bromide, and iodide.

Note added in proof.—By using data from the "Tables of Selected Values of Chemical Thermodynamic Properties" (Nat. Bur. Standards, Washington, Circular 500, 1952) and our values of the heats of solution, we obtain $Q_f[AlCl_3(c)] = 168$; $Q_f[AlBr_3(c)] = 125·6$; $Q_f[AlI_3(c)] = 30·5$ kcal./mole. Differences in the figures shown in Table 3 arise mainly from the new values of the dissociation energy of fluorine and the heat of sublimation of aluminium. The values of K thus become 86, 73, and 42 for chloride, bromide, and iodide respectively, and the value of $D(N–Al)$ is raised by $\sim$6 kcal.

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THE UNIVERSITY, BRISTOL. [*Received, December 11th*, 1953.]

NOTES.

Determination of Electrokinetic Charge and Potential by the Sedimentation Method. Part VII. Silica in Some Solutions containing Multivalent Anions.*

By C. I. DULIN and G. A. H. ELTON.

[Reprint Order No. 4712.]

ELECTROKINETIC charges and potentials have been determined by the sedimentation method for fused silica powder in dilute aqueous solutions of sulphuric acid, potassium sulphate, potassium ferricyanide, and potassium ferrocyanide. The procedure was similar to that previously described, but an improved method of smoothing the sedimentation results was used. Various workers (see, *e.g.*, Rutgers and de Smet, *Trans. Faraday Soc.*, 1945, **41**, 758; 1947, **43**, 102; Buchanan and Heymann, *J. Colloid Sci.*, 1949, **4**, 151) have found experimentally that the electrokinetic potential of many systems varies linearly with the logarithm of the electrolyte concentration, and Robinson (*J. Chem. Physics*, 1946, **14**, 721) has given a tentative theoretical explanation of this effect. A study of our previous results for silica (Parts I, III, and V, *J.*, 1952, 286; 1953, 1168, 2099) shows that this rule is obeyed by silica in solutions containing univalent cations, but not in those containing multivalent cations, where cation hydrolysis is possible. The expression relating the

* Part VI, *J.*, 1953, 3690.

electrokinetic potential, ζ, with the charge, σ, is that given by Benton and Elton (*J.*, 1953, 2096), *viz.*,

$$\sigma = \left[\frac{\varepsilon kT}{2\pi}\right]^{\frac{1}{2}} [\Sigma n_i (e^{-z_i e\zeta/kT} - 1)]^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where n_i is the number of ions of type i per unit volume of the bulk solution, z_i is the valency, ε is the dielectric constant in the diffuse layer, k is Boltzmann's contsant, e is the electronic charge, and T is the absolute temperature. For fairly large values of ζ (of the order of 100 mv, as obtained with univalent cations), the contribution of terms due to anions (from solvent, solute, or hydrolysis products) is negligible (see Part III, *loc. cit.*), and $e^{e\zeta/kT} \gg 1$, so that equation (1) reduces to

$$\sigma^2 = Ace^{e\zeta/kT} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where A is a constant, and c is the normality. Also

$$\zeta = M \log c + N \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where M and N are constants. The charge is related to the sedimentation velocity, u, by the expression

$$\sigma^2 = B\kappa(1/u - 1/u_0) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where B is a constant, κ is the specific conductivity of the suspension used, and u_0 is the limiting velocity. In solutions of sufficient concentration to render negligible the contribution of the solvent to the conductivity of the suspension, we may assume that κ is proportional to c over moderate ranges of concentration, *i.e.*, that the equivalent conductivity does not vary greatly over the range. With this assumption, we obtain from (2), (3), and (4)

$$\log (1/u - 1/u_0) = P \log c + Q \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where P and Q are constants. The data for all solutions with univalent cations fit this equation well, and good straight lines are obtained when $\log (1/u - 1/u_0)$ is plotted against $\log c$, slight deviations occurring at the lowest concentrations, owing to the increasing relative contribution of the solvent to the conductivity of the suspension. The best straight line may be determined by the method of least squares, and this method is particularly useful for smoothing results obtained in the higher concentration ranges, where u is not very different from u_0. The results given in the Table for the electrolytes with multivalent anions were calculated from data smoothed in this way.

It is seen that the charge in sulphuric acid is 200—600 e.s.u. less than that in potassium sulphate solution, owing to the fact that in acid solution the contribution of ions from the solvent to the electrokinetic charge is largely suppressed (see Parts III and V, *locc. cit.*). The charges and potentials for sulphuric acid are similar to those previously reported for hydrochloric and nitric acids, while those for potassium sulphate, ferricyanide, and ferrocyanide are similar to those for potassium chloride and nitrate. These results indicate that, as is usually found, the valency of the anion has little effect on the magnitude of the charge and potential for a negatively charged surface, the important factor being the valency of the cation.

	σ, e.s.u./cm.^{2}				ζ, mv			
c, N	H_2SO_4	K_2SO_4	$K_3Fe(CN)_6$	$K_4Fe(CN)_6$	H_2SO_4	K_2SO_4	$K_3Fe(CN)_6$	$K_4Fe(CN)_6$
1×10^{-3}	3488	3792	3706	3489	95·4	98·8	98·6	95·7
5×10^{-4}	2916	3498	3218	3150	103·8	112·7	109·2	108·2
2×10^{-4}	2226	2721	2731	2578	113·3	123·4	122·6	120·9
1×10^{-4}	1805	2148	2223	2140	120·2	129·1	129·2	128·1
5×10^{-5}	1453	1765	1752	1750	126·9	136·8	135·4	135·4
2×10^{-5}	1093	1299	1328	1364	135·8	144·2	145·1	145·9
1×10^{-5}	878	1080	1190	1130	142·3	153·0	155·3	154·0

All values of charge and potential are negative.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, October 9th*, 1953.]

Chemical Reactions of Complexes. Part VI. Dinuclear Dihydrazide–Nickel Complexes.*

By Luigi Sacconi.

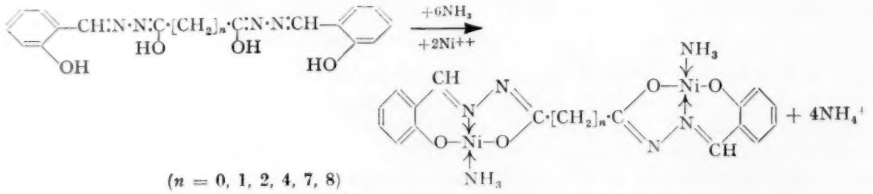
[Reprint Order No. 4853.]

Dihydrazones obtained by condensation of aliphatic dicarboxydihydrazides with salicylaldehyde, 2-hydroxy-1-naphthaldehyde, *o*-aminobenzaldehyde, or *o*-hydroxyacetophenone, have tautomeric formulæ :

$$HY{\cdot}Ar{\cdot}CX{:}N{\cdot}NH{\cdot}CO{\cdot}[CH_2]_n{\cdot}CO{\cdot}NH{\cdot}N{:}CX{\cdot}Ar{\cdot}YX = HY{\cdot}Ar{\cdot}CX{:}N{\cdot}N{:}\underset{HO}{C}{\cdot}[CH_2]_n{\cdot}\underset{OH}{C}{:}N{\cdot}N{:}CX{\cdot}Ar{\cdot}YX$$

(Ar = C_6H_4 or $C_{10}H_6$; X = H or Me; Y = O or NH; n = 0, 1, 2, **4**, **6**, 7, or 8)

They react in their enolic forms with nickel acetate in aqueous-alcoholic ammonia as bistridentate complexing agents, forming dinuclear dihydrazido-diammine–dinickel complexes, exemplified as follows for salicylaldehyde :

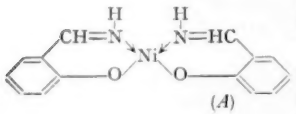


(n = 0, 1, 2, 4, 7, 8)

The formation of the complexes may be assisted by the conjugation in the imidic forms, =N·Ċ·O–, necessarily involved in the complexing.

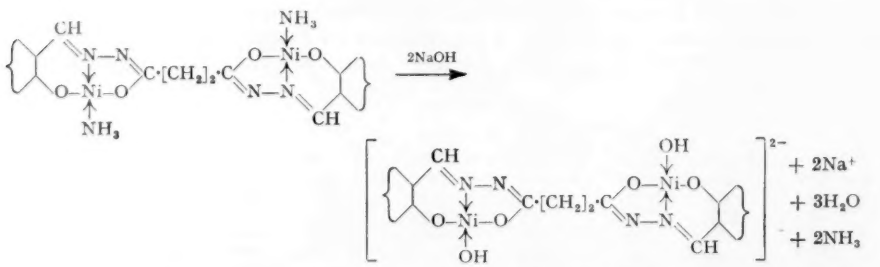
The complexes are very sparingly soluble in water and inert organic solvents. At >200° they give off ammonia. They are diamagnetic, indicating that the nickel central atoms are in the dsp^2 square-planar state (Pauling, *J. Amer. Chem. Soc.*, 1931, **53**, 1367).

If the nickel acetate in ammonia is brought in reaction with compounds R·CH:N·N:CH·R and the aldehydes or the ketone, then imino-derivatives of type (*A*) are formed.



(*A*)

If treated with aqueous-alcoholic sodium hydroxide, the dinuclear complexes lose ammonia, forming the alkaline salts of the hydroxo-complexes, exemplified below. This complex is very stable towards alkali and insoluble in water and organic solvents. It is diamagnetic and therefore planar with respect to the four dsp^2 covalent bonds.



Experimental.—Hydrazones. An aqueous or aqueous-alcoholic solution of the dihydrazide (1 mol.) was heated with the aldehyde or ketone (*ca.* 2—2·5 mols.), dissolved in alcohol, on the water-bath for ½—1 hr. The *dihydrazone* separated. By addition of water larger yields were

* Part I, *J. Amer. Chem. Soc.*, 1952, **74**, 4503; Part II, *Z. anorg. Chem.*, 1953, **271**, 176; Parts III and IV, *Gazzetta*, 1953, **83**, 884, 894; Part V, *Z. anorg. Chem.*, in the press.

obtained. The products (Table 1) were yellow, except for the first three and the last, which were colourless, and were sparingly soluble in aqueous-alcoholic ammonia or sodium hydroxide in which they gave yellow solutions.

TABLE 1. *Dihydrazones*, HY·Z·CX:N·NH·CO·$[CH_2]_n$·CO·NH·N:CX·Z·YH.

X	Y	Z	*n*	M. p.	Found, N (%)	Formula	Reqd., N (%)
H	O	C_6H_4	0	310° *	17·6	$C_{16}H_{14}O_4N_4$	17·2
			7	190—191	12·9	$C_{23}H_{28}O_4N_4$	13·2
			8	213—214	12·75	$C_{24}H_{30}O_4N_4$	12·8
H	O	$C_{10}H_6$ †	1	226—228 *	12·5	$C_{25}H_{20}O_4N_4$	12·7
			2	277 *	12·1	$C_{26}H_{22}O_4N_4$	12·3
			4	313—314 *	11·0	$C_{28}H_{26}O_4N_4$	11·6
			6	294—295	10·65	$C_{30}H_{30}O_4N_4$	11·0
			7	244—245	11·0	$C_{31}H_{32}O_4N_4$	10·7
			8	227—229	10·4	$C_{32}H_{34}O_4N_4$	10·4
Me	O	C_6H_4	0	311—312 *	15·8	$C_{18}H_{18}O_4N_4$	15·8
			2	250—252 *	14·9	$C_{20}H_{22}O_4N_4$	14·7
			8	208—209	12·1	$C_{26}H_{34}O_4N_4$	12·0
H	NH	C_6H_4	1	225—229 *	24·35	$C_{17}H_{18}O_2N_6$	24·8
			6	216—217	20·5	$C_{22}H_{28}O_2N_6$	20·6
			8	191—192	19·3	$C_{24}H_{32}O_2N_6$	19·25

* With decomp. † From 2 : 1-HO·$C_{10}H_6$·CHO.

TABLE 2. *Ammino-complexes* (*see formula in text*).

						Found, %			Required, %		
No.	Ar	X	Y	*n*	Formula	N	NH_3	Ni	N	NH_3	Ni
1	C_6H_4	H	O	0	$(C_{16}H_{10}O_4N_4)(NH_3)_2Ni_2$	17·25	—	24·7	17·7	—	24·8
2	,,	,,	,,	1	$(C_{17}H_{12}O_4N_4)(NH_3)_2Ni_2$	—	7·2	24·0	—	7·0	24·1
3	,,	,,	,,	2	$(C_{18}H_{14}O_4N_4)(NH_3)_2Ni_2$	16·7	—	23·4	16·75	—	23·4
4	,,	,,	,,	4	$(C_{20}H_{18}O_4N_4)(NH_3)_2Ni_2$	—	6·4	22·2	—	6·4	22·15
5	,,	,,	,,	7	$(C_{23}H_{24}O_4N_4)(NH_3)_2Ni_2$	14·5	—	20·45	14·7	—	20·5
6	,,	,,	,,	8	$(C_{24}H_{26}O_4N_4)(NH_3)_2Ni_2$	—	5·9	19·85	—	5·8	20·0
7	$C_{10}H_6$ *	,,	,,	1	$(C_{25}H_{16}O_4N_4)(NH_3)_2Ni_2$	13·9	—	20·1	14·3	—	20·0
8	,,	,,	,,	2	$(C_{26}H_{18}O_4N_4)(NH_3)_2Ni_2$	—	5·6	19·3	—	5·7	19·5
9	,,	,,	,,	4	$(C_{28}H_{22}O_4N_4)(NH_3)_2Ni_2$	12·8	—	18·2	13·35	—	18·6
10	,,	,,	,,	6	$(C_{30}H_{26}O_4N_4)(NH_3)_2Ni_2$	12·5	—	17·9	12·8	—	17·8
11	,,	,,	,,	7	$(C_{31}H_{28}O_4N_4)(NH_3)_2Ni_2$	—	5·0	17·3	—	5·1	17·5
12	,,	,,	,,	8	$(C_{32}H_{30}O_4N_4)(NH_3)_2Ni_2$	12·3	—	17·05	12·25	—	17·1
13	C_6H_4	,,	NH	1	$(C_{17}H_{14}O_2N_6)(NH_3)_2Ni_2$	—	7·0	24·1	—	7·0	24·2
14	,,	,,	,,	2	$(C_{18}H_{16}O_2N_6)(NH_3)_2Ni_2$	—	6·6	23·3	—	6·8	23·5
15	,,	,,	,,	6	$(C_{22}H_{24}O_2N_6)(NH_3)_2Ni_2$	19·7	—	20·9	20·1	—	21·1
16	,,	,,	,,	8	$(C_{24}H_{28}O_2N_6)(NH_3)_2Ni_2$	—	5·6	20·2	—	5·8	20·1
17	,,	CH_3	O	0	$(C_{18}H_{14}O_4N_4)(NH_3)_2Ni_2$	16·55	—	23·35	16·7	—	23·4
18	,,	,,	,,	2	$(C_{20}H_{18}O_4N_4)(NH_3)_2Ni_2$	14·9	—	20·7	14·85	—	20·75
19	,,	,,	,,	8	$(C_{26}H_{30}O_4N_4)(NH_3)_2Ni_2$	13·6	—	19·1	13·7	—	19·1

* From 2 : 1-HO·$C_{10}H_6$·CHO.

Products from salicylaldehyde and adipohydrazide and from *o*-aminobenzaldehyde and succinohydrazide, were not pure. Those from salicylaldehyde and malono- and succinohydrazide were prepared by Blanksma and Bakels (*Rec. Trav. chim.*, 1939, **58**, 497).

Preparation of the complexes. A suspension of the hydrazone in alcohol was added to a solution of nickel acetate (*ca.* 2·5 mols.) in concentrated aqueous ammonia (1 g. in 10—15 ml.). Heating on the water-bath gave a red-brown solution from which the *complex* was precipitated. After cooling, this was filtered off, washed with alcohol and ether, and dried (P_2O_5). Yields were good. The dried samples were usually pure. Nickel was determined as nickel–dimethylglyoxime, ammonia by the micro-Kjeldahl method. Colours and forms of the complexes were : nos. **1**, **7**, **11**, **18**, orange needles; **2**, **4**, red plates; **3**, **16**, reddish-orange plates; **6**, **9**, **10**, orange-yellow needles; **13**, brown plates; **14**, reddish-brown plates; **15**, red prisms; **8**, **12**, **17**, **19**, orange; **5**, orange-yellow.

*Sodium dihydroxo-*N'N'''*-di-*(2*-hydroxy-*1*-naphthylmethylene*)*succinylhydrazinodinickelate.* The corresponding ammino-complex (0·4 g.), suspended in aqueous-alcoholic 4% sodium hydroxide (4 ml.), was mixed with alcohol (30 ml.) and boiled on the water-bath for a few minutes. Water (10 ml.) was added, precipitating the *hydroxo*-complex (0·3 g.) (Found, in air-dried sample : N, 8·1; Ni, 16·7; Na, 6·6. $C_{26}H_{20}O_6N_4Ni_2Na_2,3H_2O$ requires N, 8·0; Ni, 16·7; Na, 6·7%).

Susceptibility measurements. These were made by means of the modified Bhatnagar balance (Sacconi, *Atti Accad. Lincei*, 1949, **6**, 639; Bhatnagar and Mathur, *Phil. Mag.*, 1929, **8**, 1041). The diamagnetism of the complexes was beyond doubt, but individual results are not reported because of the difficulty of removing paramagnetic impurities.

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Some Derivatives of Pyridinecarboxyhydrazides.

By D. D. LIBMAN, D. L. PAIN, and R. SLACK.

[Reprint Order No. 4879.]

THE derivatives of pyridine-3- and -4-carboxyhydrazide listed in the Table have been prepared for antitubercular tests. The following methods have been used: (I) Reaction of quaternary salts of ethyl nicotinate and *iso*nicotinate with hydrazine hydrate in ethanol (cf. Yale, Losee,

No.	Compound	Method	M. p.	Appearance	Solvent
Pyridine-4-carboxyhydrazide.					
1	Dodecyliodide	I	109—111°	Orange needles	EtOH
2	*N''*-Acetyl methiodide	III	208—209	Orange prisms	MeOH
3	*N''N''*-Diacetyl methiodide [a]	III	172	Yellow plates	EtOH
4	*N''*-Acetyl dodecyliodide	III	175	Pale yellow plates	,,
5	*N''N''*-Diacetyl dodecyliodide [a]	III [b]	287 [c]	Yellow plates	,,
6	*N''*-Acetyl benzylchloride	III	245 [c]	Colourless needles	MeOH
7	*N''-iso*Propylidene methiodide	IV	198—200	Yellow prisms	90% EtOH
8	*N''-iso*Propylidene dodecyliodide	IV	107—110	Yellow needles	EtOAc
9	*N''*-Furfurylidene methiodide	IV	250	Yellow needles	MeOH
10	*N''-p*-Methylbenzylidene	II	190	Colourless plates	EtOH
11	*N''*-(5-Hydroxypentylidene)	II	131	Colourless plates	,,
12	*N''*-(2-Ethylbutylidene)	II	119—120	Colourless needles	EtOAc
13	*N''-cyclo*Pentylidene	II	170	Colourless needles	EtOH
14	[Hexamethylenebis-1-(pyridinium-4-carboxyhydrazide bromide)]	I	213—215	Orange needles	MeOH
Pyridine-3-carboxyhydrazide.					
15	Dodecyliodide	I	117—118	Pale yellow plates	EtOH
16	Methiodide	I	186	Dark red needles	Aq. MeOH
17	*N''-iso*Propylidene dodecyliodide	IV	76—77	Yellow plates	EtOAc
18	*N''-iso*Propylidene methiodide	IV	195	Pale yellow plates	EtOH

	Found (%)			Required (%)	
No.	N	Hal	Formula	N	Hal.
1	9·75	29·1	$C_{18}H_{32}ON_3I$	9·7	29·4
2	13·05	39·1	$C_9H_{12}O_2N_3I$	13·1	39·3
3	11·3	34·2	$C_{11}H_{14}O_3N_3I,\frac{1}{2}H_2O$	11·3	34·2
4	9·05	26·8	$C_{20}H_{34}O_2N_3I$	8·85	26·7
5	8·0	24·65	$C_{22}H_{36}O_3N_3I$	8·1	24·6
6	13·7	11·55	$C_{15}H_{16}O_2N_2Cl$	13·7	11·6
7	13·1	40·9	$C_{10}H_{14}ON_3I$	13·2	39·8
8	8·75	27·25	$C_{21}H_{36}ON_3I$	8·9	26·9
9	11·7	35·7	$C_{12}H_{12}O_2N_3I$	11·75	35·6
10	17·9	—	$C_{14}H_{13}ON_3$	17·6	—
11	18·65	—	$C_{11}H_{15}O_2N_3$	19·0	—
12	19·6	—	$C_{12}H_{17}ON_3$ [d]	19·2	—
13	20·5	—	$C_{11}H_{13}ON_3$ [e]	20·7	—
14	15·2	29·1	$C_{16}H_{36}O_2N_6Br_2,2H_2O$	15·1	29·1
15	9·7	29·9	$C_{18}H_{32}ON_3I$	9·7	29·4
16	14·9	45·3	$C_7H_{10}ON_2I$	15·05	45·5
17	8·8	27·0	$C_{21}H_{36}ON_3I$	8·9	26·9
18	12·8	39·7	$C_{10}H_{14}ON_3I$	13·2	39·8

[a] This structure of diacetylhydrazides is assumed (cf. Heller, Köhler, Gottfried, Arnold, and Herrmann, *J. pr. Chem.*, 1928, **120**, 49; Fox and Gibas, *J. Org. Chem.*, 1953, **18**, 1375). [b] With addition of K_2CO_3. [c] With decomp. [d] Found: C, 65·8; H, 7·5. Reqd.: C, 65·8; H, 7·8%. [e] Found: C, 65·2; H, 5·8. Reqd.: C, 65·0; H, 6·4%.

Martins, Holsing, Perry, and Bernstein, *J. Amer. Chem. Soc.*, 1953, **75**, 1933). (II) Condensation of pyridine-3- and -4-carboxyhydrazide with a carbonyl compound (*idem, loc. cit.*) or acetic anhydride. (III) Quaternation of the products from method (II) with an alkyl halide. (IV) Condensation of quaternary salts of pyridine-4-carboxyhydrazide with a carbonyl compound.

The authors thank Mr. S. Bance, B.Sc., for semi-microanalyses and the Directors of May & Baker Ltd. for permission to publish these results.

RESEARCH LABORATORIES, MAY & BAKER LTD.,
DAGENHAM, ESSEX.

[*Received, December 11th*, 1953.]

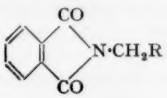
Some Reactions of Phthalimide.

By R. O. ATKINSON.

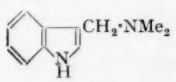
[Reprint Order No. 4942.]

PHTHALIMIDE has been found to react with formaldehyde and dimethylamine to form the base (I; R = NMe_2), which takes part in carbon alkylations in a similar manner to Mannich bases (Brewster and Eliel, "Organic Reactions," 1953, Vol. VII, p. 99), and may provide a useful method for the preparation of primary amines difficultly accessible by other means.

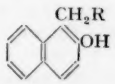
Initial attempts to form the base (I; R = NMe_2) by heating phthalimide, 40% formaldehyde solution, 30% dimethylamine solution, and acetic acid at 80° for a few minutes, or at 30° for several hours were unsuccessful, the product being *N*-hydroxymethylphthalimide (I; R = OH). The base was finally prepared by stirring the reaction mixture rapidly for 15 min. at room temperature, removing the unchanged phthalimide, and treating the filtrate with 25% sodium hydroxide solution at −10°. The yield was 76%, allowing for the recovered phthalimide.



(I)



(II)



(III)

The base (I; R = NMe_2) and the quaternary iodide (I; R = NMe_3}I) reacted with warm water to form the hydroxymethyl derivative (I; R = OH), whilst the hydrochloride in boiling alcohol gave phthalimide, thus precluding the use of these solvents as media for alkylation. The quaternary iodide with sodium cyanide in dimethylformamide gave phthalimidoacetonitrile in 81% yield.

Surprisingly, the unquaternised base, when heated with indole and a catalytic amount of sodium hydroxide at 180° for 2 hr., gave 3-phthalimidomethylindole (I; R = 3-indolyl) in 66% yield. Except for the few instances listed by Eliel (*J. Amer. Chem. Soc.*, 1953, **75**, 3589), bases which cannot undergo amine elimination and formation of an ethylenic intermediate take part in alkylation reactions only when quaternised (Snyder and Brewster, *ibid.*, 1949, **71**, 1058).

The recorded instances of nitrogen-alkylations by Mannich bases have all been amine-exchange reactions (*e.g.*, Snyder and Brewster, *ibid.*, 1948, **70**, 4230; Snyder and Eliel, *ibid.*, p. 4233; Bauer and Cymerman, *J.*, 1951, 3311). Phthalimide, which takes part readily in Michael-type additions (*e.g.*, Galat, *J. Amer. Chem. Soc.*, 1945, **67**, 1414; Atkinson and Poppelsdorf, *J.*, 1952, 2448), might be expected to react with Mannich bases and thus provide another route to certain primary amines.

Phthalimide and catalytic quantities of sodium hydroxide, heated with gramine (II) or 1-dimethylaminomethyl-2-naphthol (III; R = NMe_2) *in vacuo* at 180°, gave 3-phthalimidomethylindole (I; R = 3-indolyl) and 1-phthalimidomethyl-2-naphthol (III; R = phthalimido) in 82% and 69% yield respectively.

Potassium phthalimide with the methiodide (I; R = NMe_3}I) in dimethylformamide solution gave diphthalimidomethane in 75% yield.

Since this work was completed the author learned (Hellmann, *Angew. Chem.*, **1953**, **65**, 473) that kynuramine has been prepared recently by treating the Mannich base of *o*-aminoacetophenone with phthalimide and hydrolysing the product (U. Renner, Thesis, Tubingen, 1953).

Experimental.—*N-Dimethylaminomethylphthalimide.* Phthalimide (147 g.), 30% dimethylamine solution (150 c.c.), acetic acid (150 c.c.), and 40% formaldehyde solution (85 c.c.) were stirred together rapidly for 15 min. at room temperature. The unchanged phthalimide (99 g.) was removed, and the filtrate, cooled to −10°, was neutralised with 20% sodium hydroxide solution. The crystalline *base* was filtered off, washed with water, and recrystallised from alcohol, to give 50 g. (77%), m. p. 74—75° (Found: C, 64·4; H, 6·1; N, 13·5. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%).

The *methiodide*, obtained by refluxing the base in ether with an excess of methyl iodide, formed yellow crystals (70%), m. p. 239—240° (decomp.) (Found: N, 8·0; I^-, 34·7. $C_{12}H_{15}O_2N_2I$ requires N, 8·1; I^-, 33·5%). The *hydrochloride*, obtained in ether (yield 100%), had m. p. 154—155° (Found: N, 11·4; Cl^-, 14·6. $C_{11}H_{13}O_2N_2Cl$ requires N, 11·2; Cl^-, 14·8%).

Reaction of the base with water and alcohol. The base, heated with one mol. of acetic acid and water for 12 hr. at 30°, gave an almost quantitative yield of *N*-hydroxymethylphthalimide, m. p. 141—142° (Found: C, 67·1; H, 4·4; N, 8·6. Calc. for $C_9H_7O_3N$: C, 67·0; H, 4·3; N, 8·7%). Similar treatment of the hydrochloride in alcohol gave phthalimide, m. p. and mixed m. p. 242°.

Phthalimidoacetonitrile. A solution of the methiodide (6·9 g.) and sodium cyanide (1 g.) in dimethylformamide was heated under reflux for 1 hr., after which evolution of dimethylamine ceased. Dilution with water (60 c.c.) precipitated the crude nitrile, m. p. 118—120°. Recrystallisation from boiling water gave silky needles (3·1 g., 81%), m. p. 123—124° (Found: N, 14·9. Calc. for $C_{10}H_6O_2N_2$: N, 15·0%). Hydrolysis in acetic acid–hydrochloric acid (3 : 1) gave phthaloylglycine, m. p. 190—191° (Found: N, 6·8. Calc. for $C_{10}H_7O_4N$: N, 6·8%).

3-*Phthalimidomethylindole.* (*a*) The base (I; R = $CH_2{\cdot}NMe_2$) (10·2 g.) was heated with indole (5·9 g.) and a few mg. of sodium hydroxide *in vacuo* at 180° for 2 hr. The resulting glass was triturated with alcohol, to give the *compound* (8 g., 65%). A portion recrystallised from alcohol had m. p. 182—183° (Found: C, 73·9; H, 4·4; N, 10·2. $C_{17}H_{12}O_2N_2$ requires C, 73·9; H, 4·3; N, 10·2%).

(*b*) Gramine (3·5 g.), phthalimide (2·9 g.), and a little sodium hydroxide similarly gave the same product (4·5 g., 82%), m. p. and mixed m. p. 182—183°.

1-*Phthalimidomethyl-2-naphthol.* 1-Dimethylaminomethyl-2-naphthol (10 g.), phthalimide (7·5 g.), and a few mg. of sodium hydroxide were ground together and heated *in vacuo* at 180° for 1 hr., whereafter evolution of gas ceased. The mixture was cooled and triturated with alcohol, to give the crude *compound*, which recrystallised from alcohol as pale yellow prisms (10·5 g., 69%), m. p. 202—203° (Found: C, 74·0; H, 4·3; N, 4·6. $C_{19}H_{13}O_3N$ requires C, 75·2; H, 4·3; N, 4·6%).

Diphthalimidomethane. Phthalimi dotetramethylammonium iodide (6·5 g.), potassium phthalimide (3·7 g.), and dimethylform amide (20 c.c.) were heated under reflux for 6 hr., after which evolution of dimethylamine ceased. Dilution with water (20 c.c.) afforded the crude product, which was recrystallised from chloro for m–alcohol (yield, 4 g., 65%) and had m. p. 226° (Found: N, 9·2. Calc. for $C_{17}H_{10}O_4N_2$: N, 9·15 %).

Thanks are due to the Directors of The British Drug Houses Ltd. for permission to publish this note.

Production and Development Division,
The British Drug Houses Ltd., London, N.1.

[*Received, December 30th*, 1953.]

Aromaticity in Seven-membered Ring Systems.

TILDEN LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT THE IMPERIAL COLLEGE OF SCIENCE, LONDON, ON NOVEMBER 5TH, 1953, AND AT THE UNIVERSITY OF NOTTINGHAM, ON NOVEMBER 26TH, 1953.

By A. W. JOHNSON, M.A., PH.D., A.R.C.S.

LESS than ten years ago a subject closely related to that of the present discourse was treated in another Tilden lecture.[1] The extraordinary change which has occurred in the field of non-benzenoid aromatic ring systems in that short time should in itself be ample justification for reviewing the field once again, but this opinion is strengthened by the firm belief that Sir William Tilden himself would have approved the choice. He was particularly interested [2] in the structural features which conferred aromatic properties on the benzene molecule and were absent in his terpenes, even though many terpenes contained olefinic double bonds. In his long lifetime he witnessed much of the development of our modern idea of the nature of the benzene nucleus; the Kekulé formula in 1865, the Armstrong and Baeyer centric formula (I) in 1887, the Thiele "partial valency" formula (II) in 1898, Robinson's theory of the "aromatic sextet," and finally in the thirties,[3] the molecular-orbital treatment of benzene by Hückel who associated aromatic stability with the presence of six (but not four or eight) π-electrons in a closed ring system.

(I)

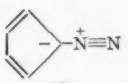
(II)

(III)

An important consequence of a theoretical approach such as this to a structural problem is the inspiration given to experimental work once the theoretical implications have been appreciated. It is sufficient to recall that ten years ago the tropolone ring system was unknown and that the earlier German reports on *cyclo*octatetraene chemistry were still private documents of the I.G. Farbenindustrie, to emphasise the immense effort which has been put into this branch of experimental organic chemistry in the last decade.

Although *cyclo*butadiene (III) still eludes us, the *cyclo*octatetraene molecule (IV) is known to be puckered and its physical and chemical properties [4] indicate that the double bonds are largely olefinic in character. *cyclo*Pentadiene and *cyclo*heptatriene, which contain an odd number of carbon atoms in the ring and therefore are not fully conjugated, can, in the form of their ions, fulfil the conditions necessary for achieving the aromatic state. This occurs in the anion of *cyclo*pentadiene and in the cation of *cyclo*heptatriene. The stability of the *cyclo*pentadienyl anion has been recognised for many years and its structural relation to benzene was stressed by Robinson several years ago. The recent preparation of diazo*cyclo*pentadiene (V) [5] which is stable in the presence of copper at 160°, further illustrates the point but the best example is probably the high stability and aromatic character of ferrocene (VI).[6]

(IV)



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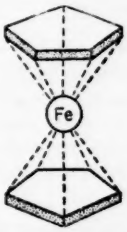
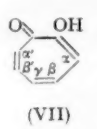


(VI)

Structures based on the *cyclo*heptatriene cation were not recognised until 1945 when Dewar [7] postulated the tropolone ring system (VII) in order to explain the aromatic properties of the non-benzenoid compound stipitatic acid (VIII), a metabolite of *Penicillium stipitatum*. Shortly afterwards [8] he incorporated the same ring system into a structure (IX) now known to be substantially correct for the alkaloid colchicine. In the years following, several other natural products containing the tropolone ring system were described. Examples include the α-, β-,

and *γ-iso*propyltropolones or thujaplicins from the heartwood of western red cedar (*Thuja plicata* D. Don) [9] and the α- and β-isomers from certain essential oils,[10] *e.g.*, those from *Chamaecyparis taiwanensis* and *Thujopsis dolabrata*; purpurogallin (X) [11] which is found as its glucosides [12] in certain galls; the mould products puberulic (XI) and puberulonic acid (XII),[13] and nootkatin (XIII),[14] another wood product, which is a tropolone containing *iso*propyl and methylbutenyl side-chains.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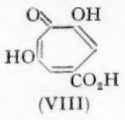
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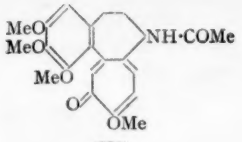
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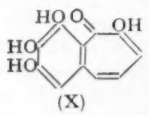
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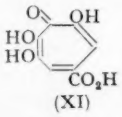
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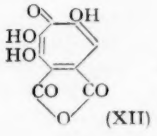
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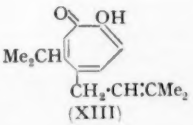
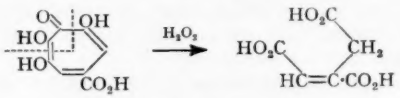
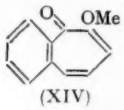

(XIII)

The existence of a tropolone nucleus in a new compound can often be deduced from examination of the ultra-violet [15] and infra-red [16] absorption spectra and also from the display of the now familiar chemical properties such as general aromatic behaviour, rearrangement by alkalis to benzenoid carboxylic derivatives, the basic properties, and the lack of ketonic reactions, which however are exhibited after hydrogenation of the ring system. Further hydrogenation yields a 1 : 2-diol which frequently can be oxidised to a dicarboxylic acid.[17] Direct oxidation of a tropolone may also provide useful results as was the case, for example, with benzotropolone,[18] the thujaplicins,[19] and stipitatic [20] and puberulic acids,[21] *e.g.*:



The carbonyl activity frequently displayed in benzotropolones—*e.g.*, αβ-benzotropolone methyl ether (XIV) forms a 2 : 4-dinitrophenylhydrazone,[18] βγ-benzotropolone (XV) and its methyl ether readily form carbonyl derivatives,[22] and the dibenzotropolone (XVI) forms a dioxime and a quinoxaline derivative [23]—is attributed to the inhibition of resonance in the tropolone ring by the reluctance of the benzene ring to assume the *o*-quinonoid configuration.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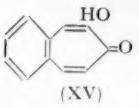
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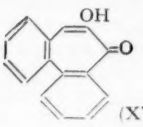
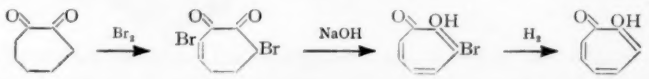

(XVI)

Once the interest in the tropolone series had been established, synthetic routes were rapidly developed and a choice of methods is now available. In the first place Cook [24] and independently Nozoe,[25] whom many of us were pleased to meet in England this autumn, have used 1 : 2-*cyclo*heptanediones as starting materials and have effected the necessary dehydrogenation with bromine. The intermediate bromotropolones can be debrominated by hydrogenolysis:

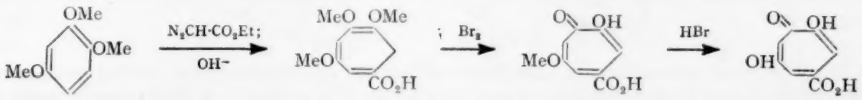


This method has been used for synthesising the three *iso*propyltropolones or thujaplicins,[26] the three methyltropolones,[27] β-ethyltropolone,[28] β- and *γ-tert.*-butyltropolones,[29] αβ-benzotropolone,[18] indano(5′ : 6′-α : β)tropolone,[30] and purpurogallin.[31] This type of synthesis generally gives good yields at the dehydrogenation step and undoubtedly represents the easiest method

of preparing tropolone itself. Nozoe and his colleagues [32] have obtained small yields of tropolone by bromination of *cyclo*heptanone with subsequent hydrogenolysis, and Knight and Cram [33] have used 2-hydroxy*cyclo*heptanone, from the acyloin condensation of pimelic ester, as the starting material. The main drawback to this type of approach is that a lengthy synthesis of the requisite *cyclo*heptane-1 : 2-dione starting material may be involved in the preparation of substituted tropolones. The isomerisation of 3 : 7-dibenzylidene*cyclo*heptane-1 : 2-dione to 3 : 7-dibenzyltropolone [34] is an interesting but not very flexible modification of this type of approach.

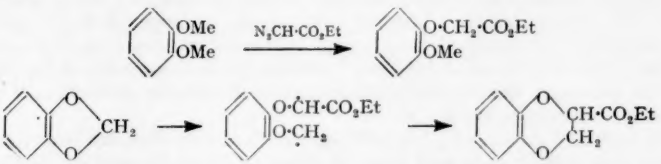
A second general method involves the ring expansion of benzenoid derivatives by use of aliphatic diazo-compounds. Thus Doering and Knox [35] have oxidised *cyclo*heptatriene, from benzene and diazomethane, with permanganate to give tropolone; and, by use of substituted benzenes, β- and γ-*iso*propyl-, β- and γ-phenyl-,[36] β- and γ-chloro-,[37] and β′ : γ-tetramethylene [36] derivatives of tropolone have been prepared, the last from tetralin.

Independently we have employed diazoacetic ester and by having the oxygen atoms of the tropolone already present in the benzene ring as methoxy-groups before the reaction we have exercised more control over the course of the oxidation, *e.g.*, in the synthesis of tropolone-β-carboxylic acid from veratrole and of stipitatic acid from 1 : 2 : 4-trimethoxybenzene : [38]

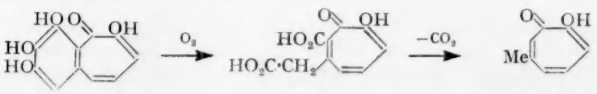


The ready availability of substituted benzenes is a factor which is greatly in favour of these methods for preparing substituted tropolones but the yields obtained are never very high although much of the unchanged benzenoid component can be recovered and used again. The use of diazoacetic ester rather than diazomethane permits the isolation of the pure crystalline intermediate *cyclo*heptatriene acids.

An interesting side reaction which is brought about when alkoxybenzenes are heated with diazoacetic ester involves the replacement of one of the *O*-alkyl groups by an ethoxycarbonylalkyl group, leading to the formation of phenoxyacetic acids.[39] This free-radical displacement reaction was further exemplified by the conversion of methylenedioxybenzene into benzodioxan-2-carboxylic ester :

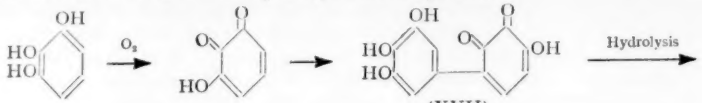


Apart from the general methods of synthesis, Haworth [40] (see also Nozoe [41]) has degraded purpurogallin to β-methyltropolone on a relatively large scale by oxidation of the benzene ring and decarboxylation of the resulting dicarboxylic acid :



The mechanism of the formation of purpurogallin from pyrogallol has also been discussed,[42] and it is postulated that pyrogallol undergoes self-condensation, possibly *via* 3-hydroxy-*o*-benzoquinone to the hydroxylated phenyl-*o*-benzoquinone derivative (XVII). As the formation of purpurogallin from pyrogallol operates in neutral or weakly acid solution it was proposed that (XVII) on acid hydrolysis might give (XVIII) which on cyclisation and loss of formic acid should yield purpurogallin. The theory, admittedly speculative, would explain the formation of purpurogallin monoethyl ether from pyrogallol and its ethyl ether and of

purpurogallin-β-carboxylic acid from pyrogallol and gallic acid,[43] and the non-formation of a purpurogallin derivative from 1 : 2-dihydroxy-3-methoxybenzene.



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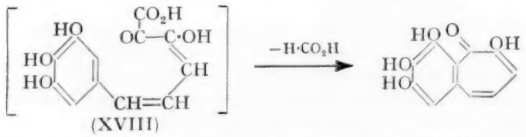
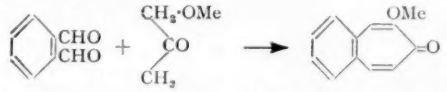


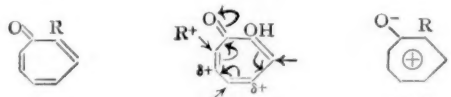
(XVIII)

It is remarkable that no syntheses of simple tropolones exist which comprise the formation of the ring by the condensation of aliphatic compounds. Tarbell [44] and independently Fernholz [45] have prepared βγ-benzotropolone by the condensation of acetol or its ethers with phthalaldehyde but attempts to apply this synthesis to maleic dialdehyde failed, *m*-hydroxybenzaldehyde being the only condensation product isolated.[46] Similarly the reaction of nitromalondialdehyde and diacetyl gave no tropolone derivatives, and a number of other negative condensations of this general type have been reported.



Many physical measurements have been carried out on tropolone and related compounds and provide a clear picture of the fine structure of the ring system. *X*-Ray measurements on the copper derivative of tropolone [47] show that the carbocyclic ring system is an almost regular heptagon with a C–C distance of 1·4 Å, suggesting quite strong aromatic character. The heat of combustion has been determined by several workers, and from this the resonance energy can be calculated, the latest value [48] being 33—36 kcal./mole, which is of the same order as calculated values [49, 50] and compares with the value of 36 kcal./mole for benzene. The *X*-ray measurements also show that the copper atom is not symmetrically placed with regard to the two oxygen atoms which can therefore be differentiated at any particular moment. This agrees with the results of a theoretical analysis of the infra-red spectrum of tropolone [50] as well as the electron-diffraction pattern.[51] In tropolone itself or in a symmetrically substituted tropolone it is impossible to differentiate between the oxygen atoms on a time-average basis and a state of rapid dynamic equilibrium between the two tautomeric forms is assumed. This is facilitated by the strong hydrogen bonding between the hydrogen and the carbonyl-oxygen atom, as is apparent from many of the physical and chemical properties of the molecule, *e.g.*, the " displaced " carbonyl band at 1615 cm.$^{-1}$ and the reduced intensity of the hydroxyl band in the infra-red spectrum, the volatility, the formation of metallic derivatives,[52] the non-formation of carbonyl derivatives, and so on.

The acidic hydroxyl group (pK_a 7·0 ± 0·2 at 20° [53]) of tropolone can be acylated and alkylated and tropolone can be re-formed from its esters or ethers by acid or alkaline hydrolysis. With thionyl chloride, tropolone is converted into 2-chlorotropone (XIX; R = Cl) [54] and this compound with ammonia or amines yields the 2-aminotropones (XIX; R = NR′R″), as does tropolone methyl ether (XIX; R = OMe).[55]



(XIX) (XX) (XXI)

These replacements as well as similar reactions with hydrazine, thiols, alkoxides, and cyanides, and halide exchange give support to the view [54, 55] that tropolone, its ethers, 2-chlorotropone, and 2-aminotropone are cyclic vinylogues of a carboxylic acid, esters, acid chloride, and amide, respectively. Accordingly the observed α- and γ-orientation of the electrophilic substitution products of tropolone may be ascribed to the directive influence of the " cyclic " carboxyl group (XX). However not all of the observed reactions of tropolone and its derivatives

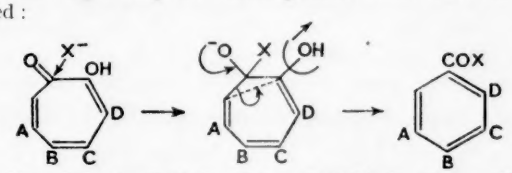
are interpreted satisfactorily by this formulation and Doering and Knox [56] have preferred to regard tropolone as (XXI; R = OH) in which the presence of the *cyclo*heptatrienylium cation is emphasised. On this basis *cyclo*heptatrienone or tropone (XXI; R = H) is the parent compound, and tropolone the *o*-phenol of the series and the hydroxyl group of tropolone plays an important rôle in the orientation and ease of substitution.

The reactions of tropolone and its homologues have been studied in great detail by Cook and by Haworth in this country and especially by Nozoe in Japan who has published, since 1949, some hundred papers on the whole field of tropolone chemistry. One of the most important of Nozoe's starting materials, β-*iso*propyltropolone or hinokitiol [57] is discarded in kilogram quantities in the form of its red ferric derivative during the purification of the essential oil of *Chamaecyparis taiwanensis*, which is used as a flotation oil in Japanese mines.

The substitution reactions of the tropolones have followed the trends already well established with benzene. The orientation was determined by linking up the various reactions by compounds such as the amino- and halogeno-tropolones formed by more than one method and then checking the orientation of these key compounds by alkaline ring-contraction to benzenoid derivatives. Of the various electrophilic substitutions, nitration,[58] halogenation,[35, 15, 59] sulphonation,[60] and hydroxymethylation [61] all cause reaction at the α- and the γ-position, as had been predicted from theoretical considerations.[49] Nitrosation [35, 62] and diazo-coupling,[24, 35, 63] however, are difficult to effect in any position other than γ and consequently the presence of a bulky group in the β-position, *e.g.*, the *iso*propyl group of hinokitiol, may affect both the ease of these reactions and the properties of the product, as in the unusual rearrangement of the azo-compounds derived from hinokitiol to the so-called hinopurpurins [64] brought about by crystallisation from ethanol:

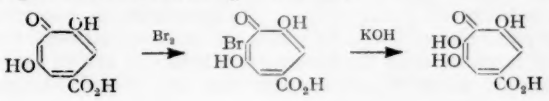
However not all of the standard aromatic reactions can be applied to the tropolone ring system, and several authors [61, 65] have reported failure to effect Friedel–Crafts substitutions, Gattermann and Kolbe reactions, and chloromethylation, undoubtedly in some of these cases because of the formation of stable intermediate tropolone complexes. Small yields of tropolone-γ-aldehyde and -γ-carboxylic acid have been obtained [65] by the action of chloroform (Reimer–Tiemann) and carbon tetrachloride respectively on tropolone in the presence of alkali, and α-allyltropolone can be prepared by the intramolecular Claisen rearrangement of tropolone *O*-allyl ether.[66]

The widespread use of the alkaline rearrangement of tropolones to derivatives of benzoic acid [35, 67] which is the basis of the interpretation of the course of the substitution reactions depends upon the observation that substituent groups, even in the α-positions, retain their relative positions in the ring during the rearrangement which is of the benzilic type and is generally represented:

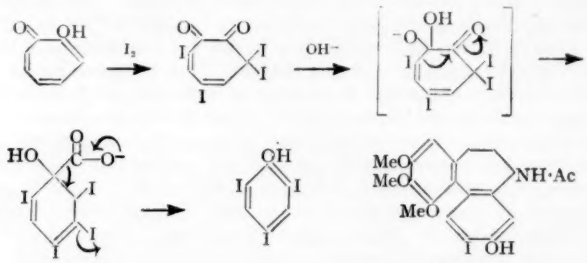


[X = OH^-, OMe^- [*e.g.*, 35, 56] H^- [65] (*e.g.*, $LiAlH_4$), R^- [68] (*e.g.*, RMgX)]

The presence of electron-attracting groups in the α- and the γ-position accentuates the electron deficiency at $C_{(1)}$ and therefore facilitates the rearrangement, *e.g.*, αγ-dinitrohinokitiol forms 2:4-dinitro-5-*iso*propylbenzoic acid with warm aqueous alcohol.[69] On the other hand puberulic acid can be largely recovered after fusion with potassium hydroxide at 300°.[70] Such vigorous alkaline conditions may of course cause side reactions such as the conversion of halogen [71] or sulphonic acid [72] substituents into hydroxyl, but this may not be always undesirable, as in a recent synthesis [73] of puberulic acid from stipitatic acid:

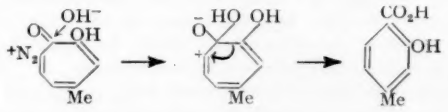


Although tropolone is a monoenolic form of a cyclic α-diketone it does not readily assume the diketo-structure and consequently the analogy of the alkaline rearrangement with the benzil–benzilic acid change is by no means complete. The formal resemblance to the benzilic rearrangement is more evident in the ring-contractions of tropolones brought about by alkalis in the presence of halogens where cyclic non-enolisable α-diketone intermediates are involved. Thus tropolone can be degraded to *sym*-tri-iodo-[35, 74] or -tribromo-phenol,[45] and colchiceine to *N*-acetyliodocolchinol (XXII) : [75]



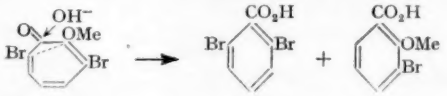
(XXII)

Concerning the direction of ring closure in the alkaline rearrangement of tropolones, the displacement of the hydride ion at $C_{(7)}$ with consequent $C_{(1-2)}$ fission is always more difficult than displacement of the $C_{(2)}$-hydroxyl or -methoxyl anion with consequent $C_{(1-7)}$ fission and the rearrangement occurs as shown above. However, if the $C_{(7)}$-hydride ion can be displaced indirectly so that a carbonium ion is formed momentarily at $C_{(7)}$, the ring closure occurs in the alternative manner with retention of the $C_{(2)}$-hydroxyl group. Such a situation occurs for example in the decomposition of diazonium salts of α-aminotropolones which gives derivatives of salicylic acid : [76]



The nitrosation of tropolones containing bulky β-substituents also leads to salicylic acids [77] and probably involves a similar type of intermediate.

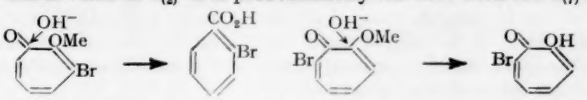
$C_{(7)}$-Carboxy-,[78] -nitro-,[79] -methyl,[61] and -phenyl [80] groups are all retained in preference to the $C_{(2)}$-hydroxyl or -methoxyl groups in the alkaline rearrangements, but with α′-halogeno-substituents cases have been reported [56, 71] where both reactions occur :



Under the influence of Grignard reagents the displacement of the bromine may be the main reaction : [68]

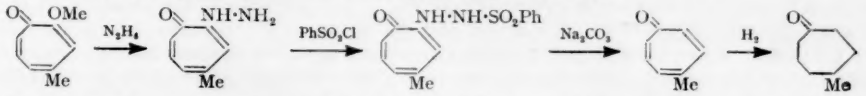
Besides attack at $C_{(1)}$, leading to ring-contraction, a nucleophilic reagent can also cause substitution at $C_{(2)}$ (or at any other position in the ring) and the relative extent of these alternative reactions at $C_{(1)}$ or $C_{(2)}$ is profoundly affected by steric factors, *i.e.*, by the nature of the α-substituents. In an ether of an unsymmetrically (α- or β-)substituted tropolone, the labile tautomerism between $C_{(1)}$ and $C_{(2)}$ is destroyed and in consequence there are two isomeric forms, *e.g.*, in the α-series (substituents at $C_{(3)}$ or $C_{(7)}$). The orientation of these ethers is conveniently accomplished by physical methods, *e.g.*, determination of dipole moments [81] or *X*-ray measurements, but chemical methods along the lines already indicated can be used. For example, in the case of the isomeric ethers of α-bromotropolone, *i.e.*, 3- and 7-bromotropolone methyl

ethers, nucleophilic displacement of the methoxy-group is more difficult in the case of the 3-isomer because of steric hindrance, and consequently the anionic attack occurs at $C_{(1)}$ (causing rearrangement), rather than at $C_{(2)}$ as is predominately the case with the $C_{(7)}$-isomer : [71]

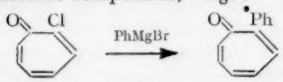


A similar situation obtains in the reaction with phenylmagnesium bromide.[68]

In the β(4 and 6)-substituted tropolone series, steric hindrance is of minor importance but Haworth and his collaborators [82] have devised a degradation of the two β-methyltropolone methyl ethers which yields the 3- and 4-methyl*cyclo*heptanones, *e.g.* :

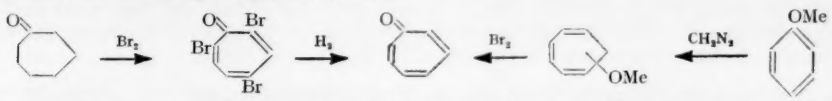


This method is one of several available for obtaining tropones (*i.e.*, hydrogen, alkyl, or aryl substituents at $C_{(2)}$) from tropolones; another is through the 2-halogenotropones by hydrogenolysis or by reaction with organometallic compounds,[83] *e.g.* :



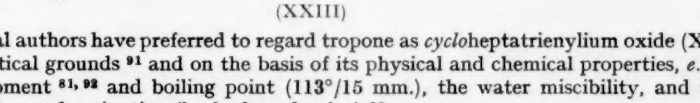
The 2-halogenotropones required for this synthesis may be obtained from tropolones by the action of thionyl chloride [54] or more conveniently by the decomposition of the hydrochlorides of the 2-hydrazinotropones with cupric salts.[84] 2-Alkyl- and 2-aryl-tropones have also been obtained from the tropolone ethers,[83, 85] copper derivatives,[83, 86] or even tropolone itself [83] with organometallic compounds.

The parent tropone, or *cyclo*heptatrienone, has been synthesised either from *cyclo*heptenone [87] or better *cyclo*heptanone [88] by oxidative bromination to 2 : 4 : 7-tribromotropone and subsequent hydrogenolysis, or alternatively, from anisole by ring expansion with diazomethane and subsequent oxidation by bromine of the methoxy*cyclo*heptatriene,[89] a method closely resembling the Cambridge tropolone synthesis :



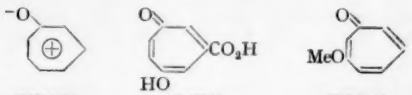
Quite recently,[90] tropinone has been degraded to tropone by elimination of the amine bridge by the Hofmann reaction, and oxidation of the dihydrotropone(s) so obtained :

In another synthetic approach to tropone,[90a] 3 : 5-dihydroxybenzoic acid has been converted into 5-hydroxymethyl*cyclo*hex-2-enone (XXIII) which yields dihydrotropone on treatment of the toluene-*p*-sulphonate with alkali.



(XXIII)

Several authors have preferred to regard tropone as *cyclo*heptatrienylium oxide (XXIV), both on theoretical grounds [91] and on the basis of its physical and chemical properties, *e.g.*, the high dipole moment [81, 92] and boiling point (113°/15 mm.), the water miscibility, and the nuclear bromination and amination (by hydroxylamine).[88]

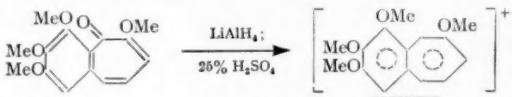


(XXIV) (XXV) (XXVI)

Substitution in the 2-position of the tropone nucleus occurs easily and thus the transition from the tropone to the tropolone series, involving the replacement of $-NH_2$ or $-Br$ by $-OH$, presents no great difficulty.[83, 86, 93] Tropone however also shows some of the properties of an unsaturated ketone : it is unstable towards alkalis, it forms Diels–Alder adducts with maleic anhydride [88] as do several of the simple tropolones,[94] and, in spite of a preliminary report to the contrary,[87] it forms an oxime, a semicarbazone, and a variety of substituted phenylhydrazones all of which are coloured crystalline solids.[88]

Very few substituted tropones lacking a 2-substituent have been described. However, the diazoacetic ester reaction with anisole gave a product which yielded tropone-4-carboxylic acid after oxidation with bromine.[95] The properties of this substance suggest a zwitterion type structure : it sublimes only with the greatest difficulty and so far it has resisted decarboxylation. In alkali it rearranges very easily to terephthalic acid. The properties of the 5-hydroxytropone-3-carboxylic acid (XXV) [96] are very similar and the syntheses of these acids led us to explore the possibility of preparing 3- and 4-hydroxytropones themselves to compare their properties with those of tropolone.* Unfortunately our work is still incomplete although we have obtained the methyl ether (XXVI), picrate, and hydrochloride of 3-hydroxytropone and there is little doubt that, like tropone itself, the other isomers of hydroxytropone will prove to be less stable and much less volatile than tropolone.

Our efforts to prepare compounds containing the *cyclo*heptatrienylium cation with no oxygen to bear the compensating negative charge, including the attractive combination of a *cyclo*heptatrienylium cation with a *cyclo*pentadienylium anion, have so far been unsuccessful and at present the only representative of this type of structure is a substituted benzo*cyclo*heptatrienylium salt (XXVII) obtained by reduction of tetramethylpurpurogallin with lithium aluminium hydride and decomposition of the product with strong acid.[97]



(XXVII)

From what is known of the properties of these *cyclo*heptatrienylium and tropone derivatives it seems that the contribution of the five-membered hydrogen-bonded ring system, with its two oxygen atoms, to the stability of tropolone is of great importance and that simplifications of the tropolone ring, while still retaining the basic *cyclo*heptatrienylium cation structure, result in a marked decrease in the aromatic character.

It gives me great pleasure to thank my Cambridge collaborators, past and present, for their loyal support, and especially Professor A. R. Todd, whose guidance and wise counsel have been a source of inspiration to all of us throughout our work.

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* Since these lectures were given, 3-hydroxytropone, m. p. 179—180°, has been isolated in the Cambridge laboratories.

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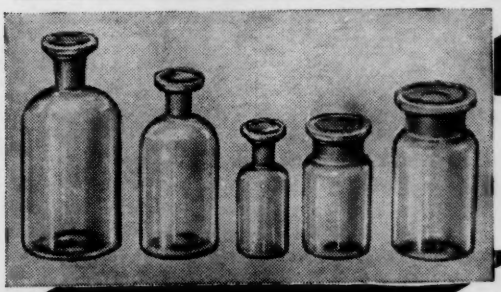

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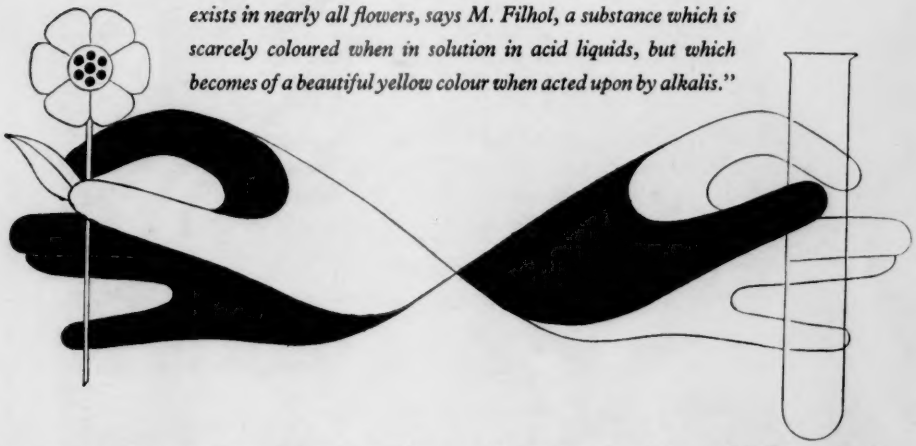

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